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Contents on Inside Cover

American Heart Journal

CONTENTS FOR DECEMBER, 1953

Original Communications

Clinical Reports

Review of Meeting

Index

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Original Communications

STUDIES OF THE EFFECT OF A SECOND DEGREE OF FREEDOM IN BALLISTOCARDIOGRAPHY

J. E. Smith, M.D.,* and Robert Rosenbaum, M.A.**

Washington, D. C.

Considerable time and effort have been expended in recent years by many research groups in an endeavor to present the clinician with a reliable method for the early detection of coronary disease. The ballistocardiograph, a device for recording the motions of the body which result from cardiac activity and subsequent blood flow, has gained increasing popularity as both a research tool and a clinical technique.

A ballistocardiogram is a graphic representation with respect to time of the motion of the body (displacement, velocity or acceleration) under the excitation of cardiovascular forces. These forces which impart motion to the body are of variable magnitude throughout the cardiac cycle. Although some investigators have attempted to measure the spatial motion of the body under the cardiovascular forces,[1-3] the most common types of ballistocardiographs (the Nickerson low-frequency table,[4] the Starr high-frequency table,[5] and the Dock leg-mounted pickup[6]) have concentrated on the measurement of the body motion in the head-foot direction.

In the literature on ballistocardiography, it has become common practice to use the term "single degree of freedom," when referring to displacement of the body along a line, "two degrees of freedom" for motion in a plane and "three degrees of freedom" for spatial motion. These terms, however, are defined differently in the established vocabulary of the physicist and the vibration engineer.

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*Chief, Medical Standards Branch Medical Division, Civil Aeronautics Administration, Washington, D. C.

**Supervisor, Dynamics & Loads Group, Aircraft Engineering Division, Civil Aeronautics Administration, Washington, D. C.

In this report, where the engineering usage is followed, the two degree of freedom system refers to two masses connected by a spring or springs. All motions referred to in this presentation are in the head-foot direction and the degrees of freedom will be (a) motion of the body in reference to a fixed point in space and (b) the motion of the platform in the Dock type leg-mounted ballistocardiograph with respect to a fixed point in space.

Dock and Taubman[6] describe a method of recording motion of the body by placing a rigid piece of metal across the shins to which a light source was attached. A photocell attached to the table responded to the motion of the body as a change in the light source. From this beginning came a variety of adaptations, all placing some kind of mass across the subject's shins with little concern for the effects upon the ballistocardiogram of the mass so placed. In our laboratory, we have noticed marked differences in the character of the ballistic record, from the same individual during the same test, when the character of the shin mass and its coupling to the shins were varied. The transducer used in these tests has been described in some detail in an earlier paper by Smith and Bryan.[7] It consists essentially of a bar-magnet velocity meter with parallel differentiating and integrating networks connected across the output of the coil. This calibrated pickup and its associated electronic amplifying and recording equipment will faithfully record simultaneously the displacement, velocity, and acceleration of the platform at all frequencies from 1 to 20 cycles per second.

EXPERIMENTAL DATA

The use of a platform on the patient's legs with a rigid suspension of the magnet shows marked variations in signal output when the weight of the platform is varied. The amplitude can be observed to increase and decrease in an individual when the mass on the legs is increased and decreased. Further, in normal individuals, with a three-pound platform placed on the skin, the amplitudes change appreciably from person to person so that normal standards are difficult to evaluate due to the wide scatter. Thus, it must be concluded that the use of a calibrated instrument has no value unless the influence of the mass of the transducer and the coupling on the legs are studied and controlled.

Twenty-five cases were studied in order to document these amplitude changes with various transducer weights. This group included normal young adults, normal older adults, several cases of healed myocardial infarcts, two cases of coarctation of the aorta, and a case of constrictive pericarditis. Tracings were taken on the legs with the transducer platform weighing three pounds, weights were added up to four pounds so that the total weight was seven pounds. Tracings were also repeated on a segment of elastic stocking between the transducer platform and the skin as it had been noted that the natural frequency of the transducer mass and coupling could be raised appreciably by this technique. Also, several cases were examined with a light mass on the skin, 5 ounces.

From this data it was determined that the natural frequency of the transducer mass at a weight of three pounds using a segment of elastic stocking could be kept above 16 cycles in all cases, and in many cases was found to be raised above

20 cycles. By the simple expedient of tightening the elastic segment the natural frequency could be raised above 20 cycles in all cases. By simply adding mass to the platform the natural frequency could easily be adjusted downward to any frequency below 20 cycles.

By using various frequencies in the second degree of freedom it was demonstrated that normal ballistic curves could be recorded in coronary heart disease which actually could be seen to be abnormal when taken with higher natural frequencies in the second degree of freedom. The same results could be observed in cases of aortic coarctation. Marked distortions of amplitude and waveform were recorded.

CASE ILLUSTRATIONS

1. A normal 31-year-old pilot (Fig. 1). *A*. The first tracing was taken using a platform and magnet weighing three pounds. A small segment of elastic stocking was placed between the platform and the skin. The natural frequency of the platform on the skin and elastic stocking combination was 20 cycles. (This frequency was obtained by attenuating the ballistic signal

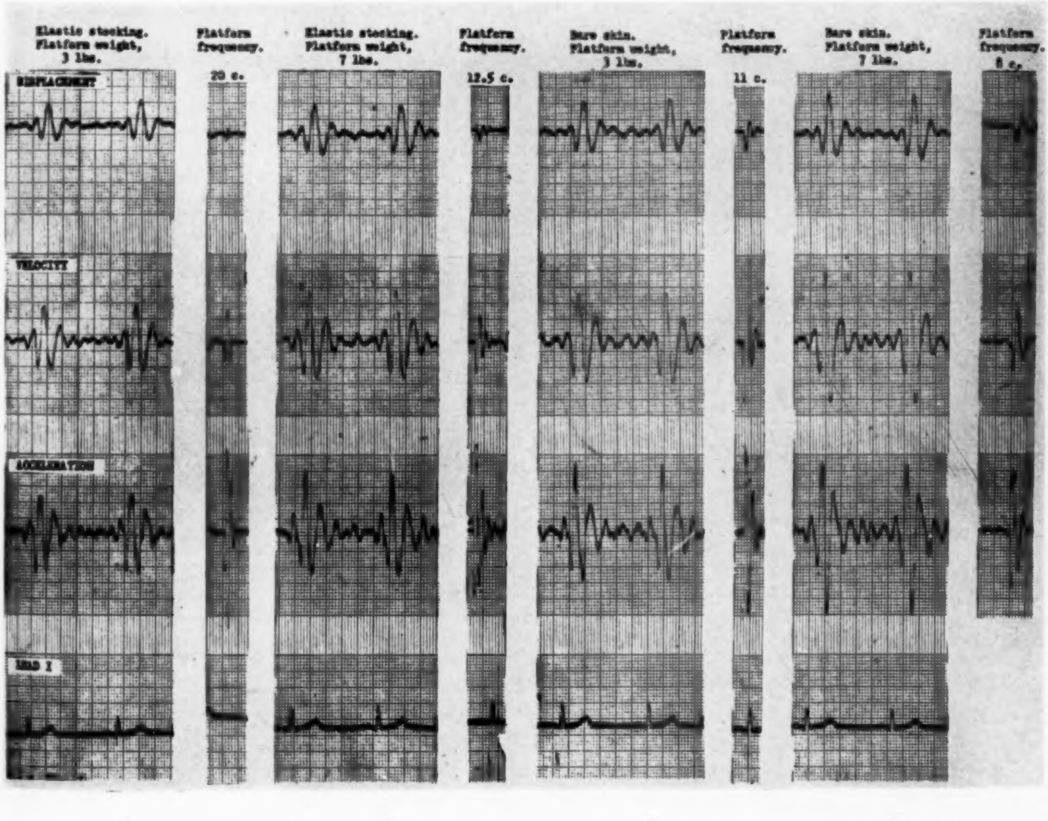

Fig. 1.—A normal 31-year-old man. *A*. Ballistocardiogram taken with 3-pound platform on elastic stocking, platform frequency 20 cycles. *B*. Tracing taken with 7-pound platform on elastic stocking, platform frequency 12.5 cycles. *C*. Tracing with 3-pound platform on skin, platform frequency 11 cycles. *D*. Tracing with 7-pound platform on skin, platform frequency 8 cycles.

and tapping the platform.) The amplitude of the displacement signal (IJ) is 0.0024 inch. *B*. By adding four pounds to the platform weight the natural frequency of the platform on the skin and elastic stocking combination has been lowered to 12.5 cycles. The amplitude of the displacement signal (IJ) is now 0.0030 inch. *C*. The three-pound platform and magnet placed on the skin shows a natural frequency of 11 cycles. The amplitude of the displacement signal (IJ) is 0.0032 inch. *D*. The seven-pound platform and magnet placed on the skin shows a natural frequency of 8 cycles. The amplitude of the displacement signal (IJ) is 0.0038 inch.

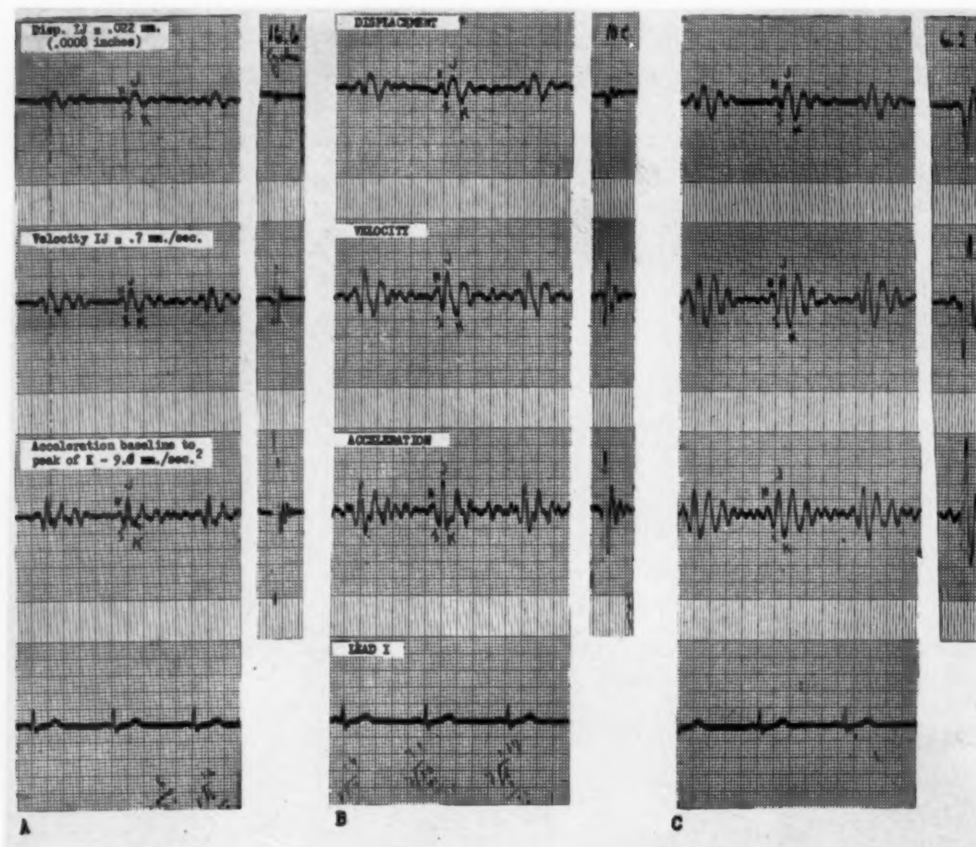

Fig. 2.—A 44-year-old ambulatory man with a healed myocardial infarct. *A*. Ballistocardiogram taken with 3-pound platform on elastic stocking, platform frequency 16.6 cycles. *B*. Tracing taken with 3-pound platform on skin, platform frequency 10 cycles. *C*. Tracing taken with 7-pound platform on skin, platform frequency 6.2 cycles. Amplitudes have increased and the tracing in *C* appears normal with loss of notched acceleration K peak seen in *A*.

The increase in the amplitude of the IJ signal with decreased natural frequency of the transducer-skin coupling provides a specific example to emphasize that a calibrated instrument, i.e., one measured with a given mass under a single condition of transducer-skin coupling, cannot be expected to yield meaningful quantitative measurement unless it is suitable for the frequencies and conditions of coupling which are encountered.

2. A 44-year-old man with a healed posterior myocardial infarct (Fig. 2). Infarction was accompanied by typical symptoms and electrocardiograph changes and occurred six months

before this tracing was taken. Patient has no symptoms at present and feels well. Blood pressure 126/70 mm. Hg.

A. Tracing was taken on skin-elastic-stocking combination with three-pound platform weight. The amplitude of the displacement (IJ) signal is 0.0008 inch. Note the notching and form changes that are present in the acceleration base line to K peak, usually seen in coronary disease. The platform frequency is 16.6 cycles.

B. The tracing was taken on the skin with a three-pound platform weight. The displacement IJ is 0.0012 inch. The acceleration K peak has increased in amplitude but notching is still present. Platform frequency is 10 cycles.

C. Tracing was taken on skin with a seven-pound platform weight. The displacement IJ signal is now 0.0016 inch and the acceleration K peak is sharp and within normal limits.

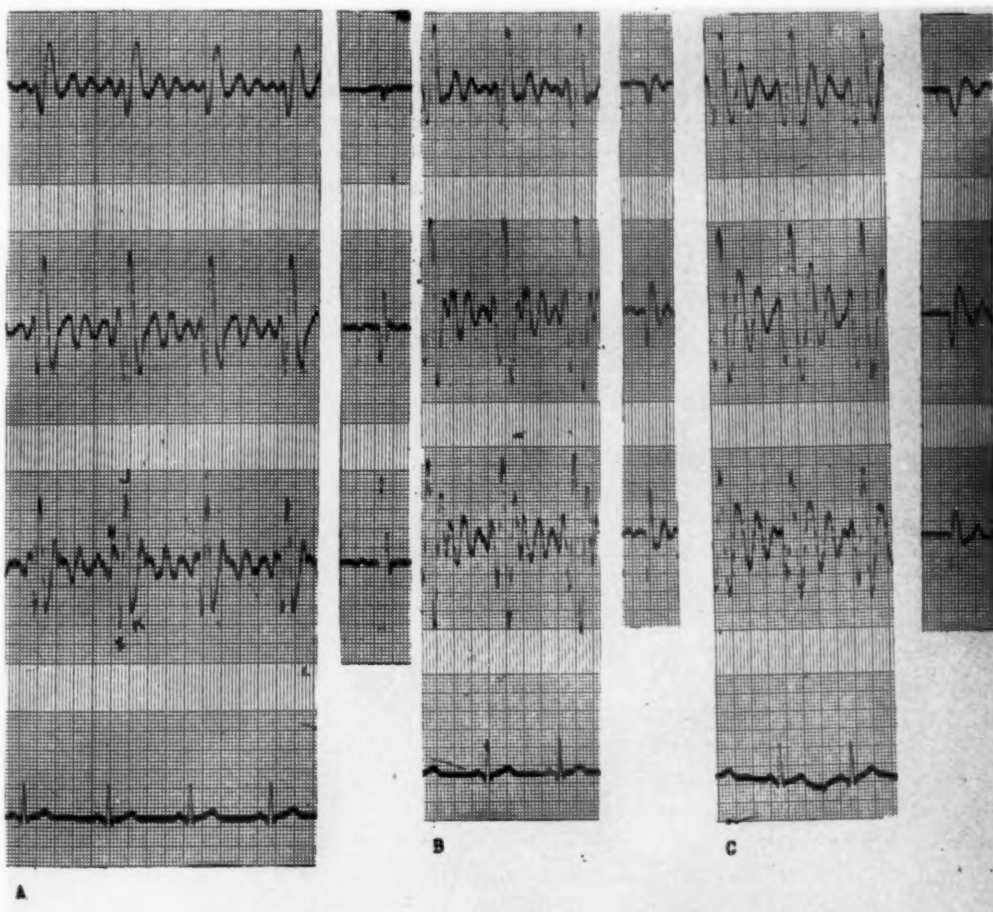

Fig. 3.—A 24-year-old man with coarctation of the aorta. *A*. Ballistocardiogram taken with 3-pound platform on elastic stocking, platform frequency 16.6 cycles. *B*. Tracing with 3-pound platform on skin, platform frequency 6 cycles. Marked amplitude increase and form distortion more obvious on the velocity and acceleration records. *C*. Tracing with 7-pound platform on skin, platform frequency 4 cycles. The blunted short K wave of *A* now appears normal in the displacement record.

On the basis of experience in this laboratory, that notching and form changes in the acceleration K peak are usually associated with coronary disease, the clinical interpretation of the record 2,*A* would be quite different from that of 2,*C*.

Also, the change in amplitude of the displacement IJ segment from 0.0008 inch in 2,*A* to 0.0016 inch in 2,*C* would now place 2,*C* in the range of normal standards.[8]

3. A 24-year-old man with aortic coarctation located two centimeters below the left subclavian artery (Fig. 3). Chief complaint, headache. Blood pressure, 180/100 mm. Hg.

A. The tracing was taken on skin-elastic-stocking combination with a three-pound platform weight. The platform frequency was 16.6 cycles. The displacement K wave shows diminished amplitude with flattening of the K peak. The amplitude of the IJ displacement signal is 0.0038 inch. The ratio of the JK to IJ segment is 73 per cent.

B. The tracing was taken on the skin with a three-pound platform weight. The platform frequency is 6 cycles. Amplitude of displacement IJ signal is 0.0054 inch. Short K wave is still present on the displacement curve.

C. The tracing taken on the skin with a seven-pound platform weight. The platform frequency is 4 cycles. The displacement K wave now has a normal appearance.

It can readily be seen from the clinical data above that a fundamental understanding of the problem is necessary. Further advancement in ballistocardiographic studies of the heart and circulation necessarily depends on more accurate analytical studies of the total instrument-body system. An attempt at this follows in the next section.

ANALYSIS

It is well known that one of the most important requirements in motion measurement is that the natural frequency of the measuring instrument should be far removed from the frequency of the motion being measured. An equally important consideration for faithful motion measurement is the requirement that the pickup itself should not appreciably alter the motion of the body whose motion is being measured. Unfortunately, recent reports in the literature indicate that little regard has been given to these fundamental principles. Designers of high- and low-frequency ballistocardiograph tables appear to have concerned themselves with developing tables with natural frequencies reasonably well removed from the approximate body natural frequency of 5 cycles per second. This approach would of course be valid if the body motion under the cardiovascular forces was at the single frequency of approximately 5 cycles. Braunstein and associates[1] have shown by Fourier wave analysis obtained from a high-frequency table that for normal persons the ballistic records indicate significant components of motion from 1 to 7 cycles. Analysis of data collected in our laboratory has shown that for abnormal cardiovascular conditions significant higher frequency components of force exist, up to 10 to 12 cycles (possibly higher). Thus, for faithful measurement of each component of motion the measuring instrument should have a natural frequency well outside the range of 1 to 12 cycles.

In the case of the leg-mounted Dock type pickup the above principle is equally applicable. The skin and elastic, viscous tissue, over the bone can be considered to be a linear damped spring, the undamped natural frequency of the pickup system being a function of the weight of the platform. Thus, the platform weight should be chosen so that the natural frequency of the platform is well outside the range of 1 to 12 cycles.

The second principle referred to above, that the measuring instrument should not alter the motion which it is attempting to measure, seems to have been lost sight of by most investigators using the leg-mounted pickup. Although this

criticism may be equally valid for the table type of ballistocardiograph the following comments are directed specifically to the users of the leg type pickup. It is common practice in the field of ballistocardiography to assume that the body when lying on a rigid table is a viscous elastic mass which acts as a simple, single-damped spring-mass system. For the case of the leg-mounted pickup the total system of the body and its associated damped spring when combined with the platform and damped skin spring can be considered to be a two degree of freedom vibrating system analogous to a vibrating system with a damped vibration absorber.[9] The function of a vibration absorber is to modify the motion of the system to which it is attached. The characteristics of a vibration absorber depend on the natural frequency of the second degree of freedom, the damping present in this degree of freedom, and the ratio of the mass of the absorber to the mass of the vibrating body to which it is attached. It can thus be seen that for the leg-mounted pickup, an indiscriminate choice of characteristics in the second degree of freedom may alter the motion of the first degree of freedom. Recent reports[10,11] of large numbers of normal ballistic records being obtained from known cardiac patients and vice versa can probably be traced to this difficulty.

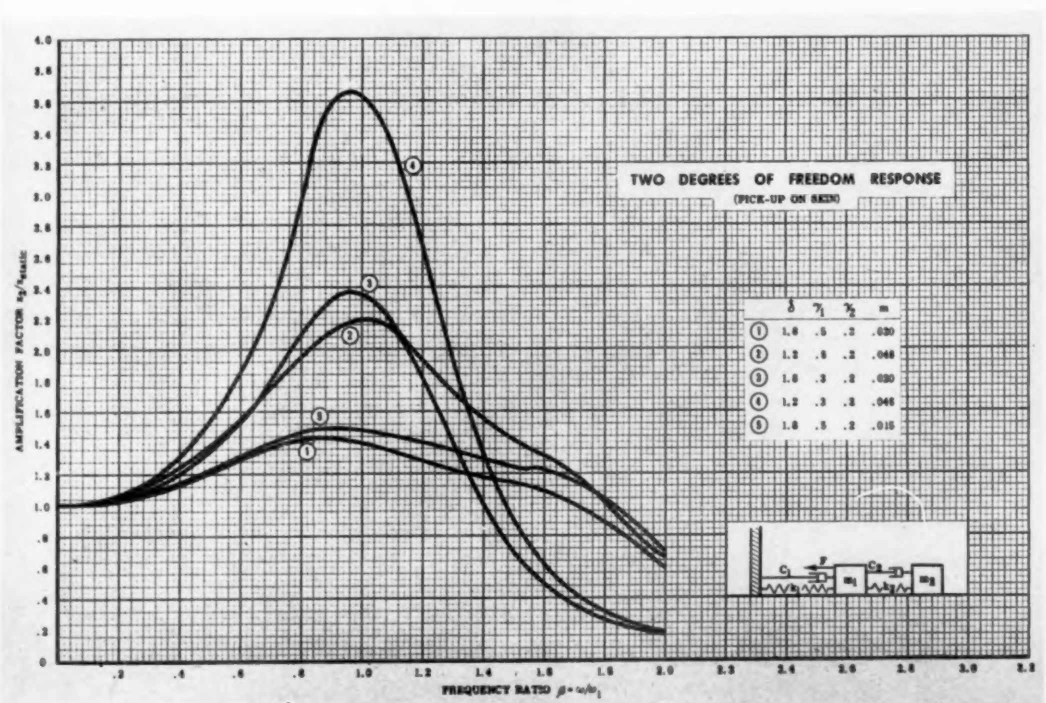

Fig. 4.—The effect of pickup frequency, body damping, and mass ratio on the response curves of the two degree of freedom system, pickup on the skin.

Consider the mechanical system represented in the insert of Fig. 4. This system is a simple representation of the body and pickup in which m_1 and m_2 are the body and pickup masses, respectively, k_1 is the spring constant of the spring between the table and body frame, k_2 the spring constant of the skin and tissue

under the platform, and c_1 and c_2 the respective viscous damping factors for the two systems. If x_1 represents the motion of the body frame relative to the fixed table and x_2 represents the motion of the bar-magnet (the coil through which the magnet moves is rigidly attached to the table) relative to the same table, then the motion of this system under the excitation of a force F applied to mass m_1 can be expressed by the following equations:

$$m_1\ddot{x}_1 + c_1\dot{x}_1 + c_2(\dot{x}_1 - \dot{x}_2) + k_1x_1 + k_2(x_1 - x_2) = F \qquad (1)$$

$$m_2\ddot{x}_2 + c_2(\dot{x}_2 - \dot{x}_1) + k_2(x_2 - x_1) = 0 \qquad (2)$$

where the dots over the x's refer to the time derivatives, i.e., $\dot{x} = dx/dt$, $\ddot{x} = d^2x/dt^2$. The force F is the cardiovascular force which is known to be acting continuously during the cardiac cycle. Such a complex periodic force can be expressed as a Fourier Series, i.e.,

$$F = \Sigma\, F_j e^{i\omega_j t} \qquad (3)$$

where F_j is the magnitude of the j component of the force and ω_j is the frequency of excitation of the j component. Since the simultaneous equations (1) and (2) are linear the motion of the system can be determined by solving the equations for each component of force separately and then summing (the principle of superposition for linear equations). It is therefore sufficient to study the effect of a single component of the force which can be expressed as $F = F_0e^{i\omega t}$. If the following substitutions are made:

$\omega_1 = \sqrt{k_1/m_1}$ = undamped natural frequency of the body

$\omega_2 = \sqrt{k_2/m_2}$ = undamped natural frequency of the platform

$\gamma_1 = c_1/c_{c1},\ \gamma_2 = c_2/c_{c2}$ = ratio of damping factor to critical damping factor for corresponding single spring mass system

$m = m_2/m_1$ = ratio of pickup mass to body mass

$\beta = \omega/\omega_1$ = ratio of forcing frequency to natural frequency of body

$\delta = \omega_2/\omega_1$ = ratio of pickup natural frequency to body natural frequency

the solutions of equations (1) and (2) are:

$$X_1 = \frac{F_0e^{i(\omega t-\varphi_1)}}{m_1\omega_1^2}\left\{\frac{[\delta^2-\beta^2]^2+4\gamma_2^2\delta^2\beta^2}{[(1-\beta^2)(\delta^2-\beta^2)-m\delta^2\beta^2-4\gamma_1\gamma_2\delta\beta^2]^2+[2\gamma_1\beta(\delta^2-\beta^2)-2\gamma_2\beta\delta(\beta^2+m\beta^2-1)]^2}\right\}^{\frac{1}{2}} \qquad (4)$$

$$X_2 = \frac{F_0e^{i(\omega t-\varphi_2)}}{m_1\omega_1^2}\left\{\frac{\delta^4+4\gamma_2^2\delta^2\beta^2}{[(1-\beta^2)(\delta^2-\beta^2)-m\delta^2\beta^2-4\gamma_1\gamma_2\delta\beta^2]^2+[2\gamma_1\beta(\delta^2-\beta^2)-2\gamma_2\beta\delta(\beta^2+m\beta^2-1)]^2}\right\}^{\frac{1}{2}} \qquad (5)$$

where φ_1 and φ_2 are the phase angles between the impressed force and the responses x_1 and x_2.

It can be seen from an examination of equation (5) that the motion of the pickup is proportional to the magnitude of the impressed force F_0 and is a function of the variables m_1, m_2, γ_1, γ_2, β and δ. Furthermore, since the spring constant

$k_1 = m_1\omega_1^2$ the expression, $F_0/m_1\omega_1^2 = F_0/k_1$, can be seen to be the displacement of the system under the force F_0 when the force is applied slowly, i.e., the static displacement of the system. The expressions x_1/x_{static} and x_2/x_{static} are thus seen to be nondimensional amplification factors.

In order to correlate the experimental data with the above analysis a plot was made of x_2/x_{static} versus β for the case of the three-pound platform on the skin of a 150 pound man, assuming the natural frequency $\omega_1 = 5$ cycles and damping $\gamma_1 = 0.5$. For this case, from the damped, free vibration of the pickup (obtained by applying a force much larger than the ballistic force and attenuating the signal to the point where the noise level was insignificant) the damping was found to be $\gamma_2 = 0.2$ and $\omega_2 \cong 9$ cycles ($\delta = 1.8$). A plot was also made of the amplification factor versus β for the same person when four additional pounds were added to the platform, in this case $\delta = 1.2$ and $m = 0.046$. These two cases are illustrated as curves (1) and (2) of Fig. 4. From an examination of these two curves it can readily be seen that if $\omega_1 = 5$ cycles per second then the response of the pickup is far from flat over the region of 0 to 10 cycles. Furthermore, although for $\delta = 1.8$ the maximum amplification factor is 1.44 at approximately $\omega = 4.5$ cycles and the minimum factor is 0.6 at 10 cycles, for the case of $\delta = 1.2$ the maximum factor is 2.2 at $\omega \cong 5.5$ cycles and the minimim factor is 0.16 at 10 cycles. Since the body damping values obtained in our laboratory indicated that body damping for most people varied between the values of 0.5 and 0.3, plots were made for the 3- and 7-pound platforms as in the previous cases except that γ_1 was chosen as 0.3, these plots are shown as curves (3) and (4) in Fig. 4. In order to study the effect of mass ratio the 3-pound platform was assumed to be placed on a 200-pound person, all other variables remaining unchanged from those used in determining curve *1* of Fig. 4, this plot is shown as curve (5) in the same figure. It can readily be seen from this figure that the ballistic record obtained from such a system would bear little resemblance to the complex impressed force. Furthermore, the distortion is a function of the variables δ, m, γ_1, as well as ω_1 and γ_2.

Clinical study indicated that the spring constant of the skin over the shin bone varied widely from person to person and that for the available platform and magnet the signal distortion due to the characteristics of the second degree of freedom would be intolerable. It was found that by application of a segment of elastic stocking over the skin (under the platform) the value of the spring constant could be raised and in fact by control of the tautness of the stocking the frequency of the 3-pound platform on the skin-stocking combination could be maintained at 20 cycles per second.

Since by the technique of the elastic stocking the effective spring constant could be maintained at 20 cycles for the 3-pound platform and could be adjusted to any lower value by adding weight to the platform, an investigation was conducted to determine the best instrumentation for the case of a 150-pound man whose body natural frequency was assumed to be 5 cycles and body damping of $\gamma_1 = 0.5$. In addition to the case of $\delta = 4$ (for $\omega_2 = 20$ cycles) the cases for weights added to the platform which would result in $\delta = 1$, 2, and 3 were investigated.

A plot of amplification factor versus frequency ratio for these cases appears in Fig. 5; curve *5* on this figure indicates the single degree of freedom case, i.e., the theoretical response of the body to the external force when no pickup is present.

An examination of the curves on Fig. 5 indicates the following:

1. The higher the value of δ the more closely does the response curve approach the single degree of freedom response.

2. The body as a single degree of freedom does not faithfully respond to the input force, i.e., the single degree of freedom response curve is not flat over the range of frequencies present in the complex cardiovascular forcing function. In the region of $\beta \leq 1$ amplification results, whereas for $\beta > 1$ the ballistic signal is attenuated.

3. For the value of $\delta = 2$, frequencies above 6 cycles are more faithfully reproduced than for the single degree of freedom. In the study of abnormal cardiovascular conditions in which higher frequency components of the forcing function may be significant, the high-frequency components can be brought out by a proper choice of platform weight.

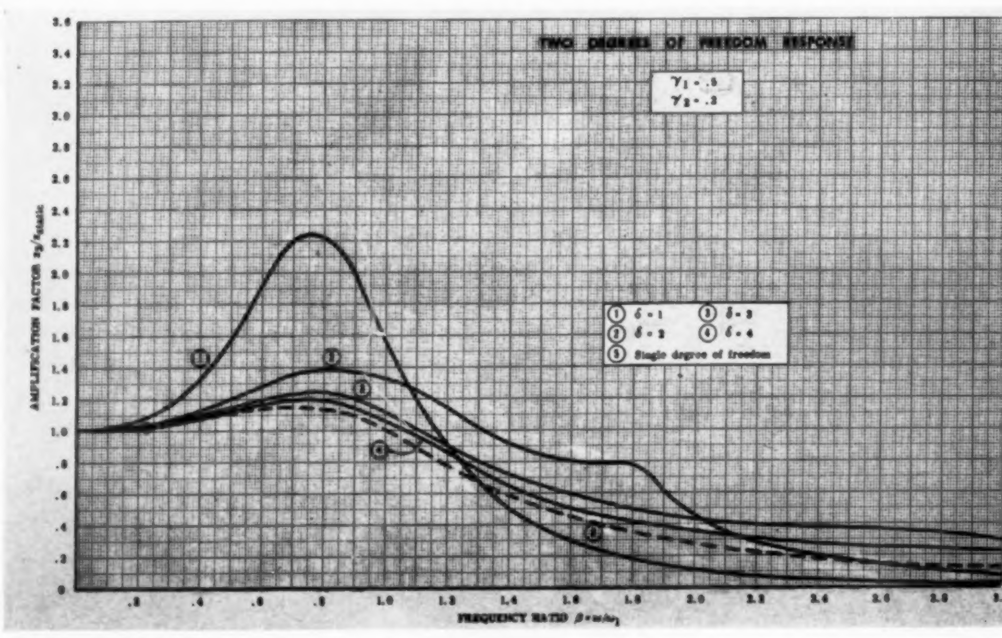

Fig. 5.—The effect of pickup frequency and mass ratio on the response curve of the two degree of freedom system compared to the single degree of freedom system Pickup on elastic stocking, body damping of 0.5 (50 per cent of critical).

Figure 6*A* shows a series of curves similar to those on Fig. 5 for similar parameters except body damping, in this case $\gamma_1 = 0.3$. It can readily be seen that for the case of $\gamma_1 = 0.3$ the distortion of the signal for all values of δ is greater than for the case of $\gamma_1 = 0.5$.

It can be seen from Figs. 5 and 6*A* that the response of the pickup can readily be altered by an indiscriminate choice of pickup weight. Although it may be possible to design a pickup and its associated equipment which would produce a signal proportional to the cardiovascular forces, the proportionality factor being constant over the significant frequency spectrum, it would appear at this

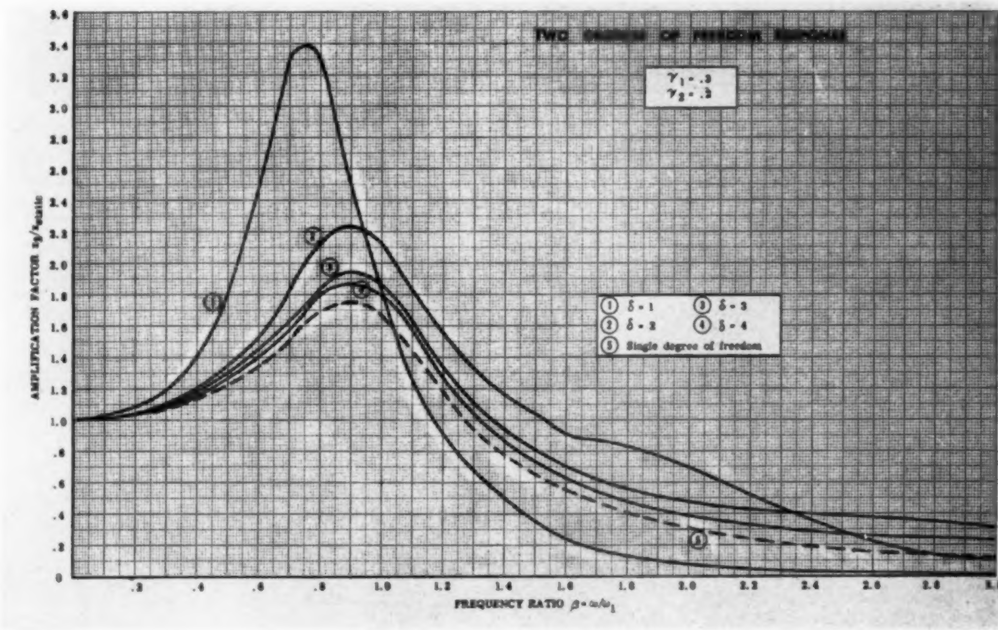

Fig. 6A.—The effect of pickup frequency and mass ratio on the response curve of the two degree of freedom system compared to the single degree of freedom system. Pickup on elastic stocking, body damping of 0.3 (30 per cent of critical).

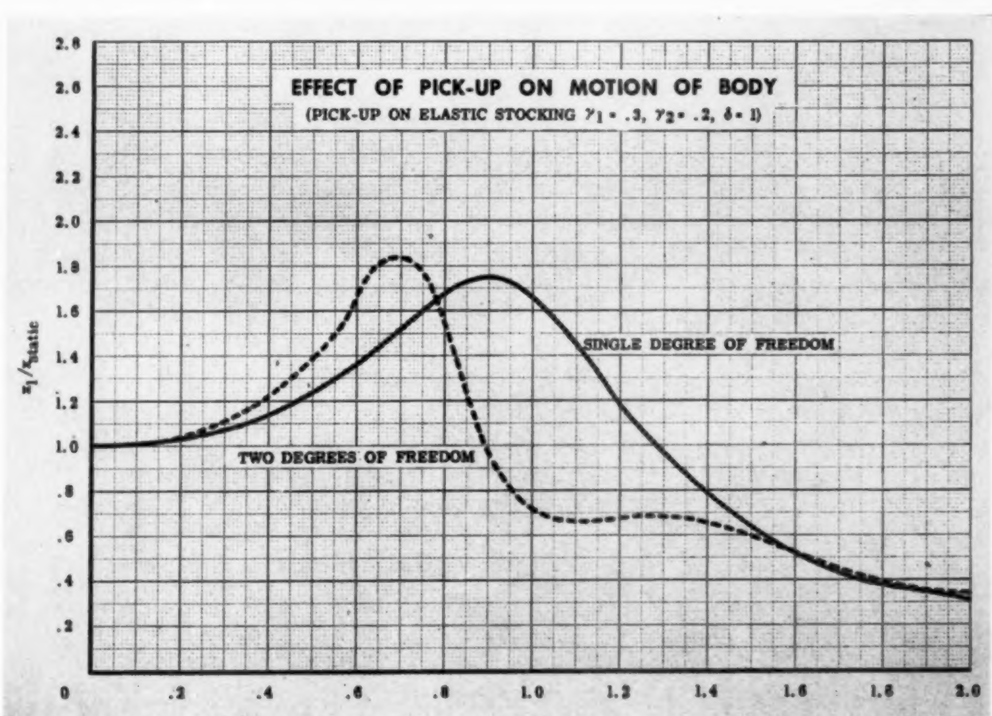

Fig. 6B.—The effect of pickup on the motion of the body to show characteristics of the pickup as a vibration absorber.

stage in the development of the ballistocardiograph that it would be simpler to obtain an instrument which would faithfully reproduce the motion of the body as a single degree of freedom under the cardiovascular forces.

Mention has been made of the possibility that the pickup may act as a tuned vibration absorber, i.e., that the pickup itself could influence the motion of the body over part of the frequency range. In order to investigate this effect, a plot of x_1/x_{ST} versus β was made for the case of $\gamma_1 = 0.3$, $\gamma_2 = 0.2$, $\delta = 1$ (Fig. 6*B*), as well as the single degree of freedom case for $\gamma_1 = 0.3$. It can readily be seen that the pickup acts as a vibration absorber over a portion of the frequency range and that at $\beta = 1$ the amplification factor is reduced from 1.65 to 0.7 by the action of the pickup.

In order to determine the value of the pickup natural frequency which would yield a faithful record (within 5 per cent), a plot of x_2/x_1 versus β for various values of δ was made (Fig. 7). Since, as the mass of the pickup is reduced and δ increased, the response of the body x_1 in the two degree of freedom system approaches the response of the body as a single degree of freedom, the plot of x_2/x_1 versus β indicates the degree of distortion of the signal in measuring the body motion. It can thus be seen from Fig. 7, that for faithful reproduction (within 5 per cent) of all components of the body motion up to 3 times the body natural frequency, the value of δ must be greater than 14. If the natural frequency of the body lies in the range of 4-6 cycles then for a $\delta = 14$, within 5 per cent all components of frequency up to 12 cycles would be faithfully reproduced. On the other hand with the instrument frequency ten times the body frequency the same accuracy could be obtained for components up to 9 cycles.

PHASE SHIFT

It is well known that the response of a damped spring mass system to a complex input forcing function may be distorted due to phase shift associated with each component of the input force. This distortion due to phase shift becomes zero only when the time delay associated with each component is constant. It can be readily be seen that a constant time delay is possible only when the phase angle varies linearly with frequency ratio β. Figure 8 contains a plot of phase shift versus β for the case of $\gamma_1 = 0.5$, $\gamma_2 = 0.2$ for $\delta = 2$ and 4, as well as a plot of φ versus β for the single degree of freedom case for $\gamma_1 = 0.5$. It is obvious that over the frequency range of interest, linear phase shift does not occur for any of the plotted curves (in fact over the range β from zero to 2.4 the curve most closely approximating linear phase shift is that for which $\delta = 2$), and that as δ increases the phase shift approaches that for the single degree of freedom. Thus as δ increases, the time delay between the motion of the body and the motion of the pickup approaches zero.

From an examination of Figs. 5, 6, 7, and 8, it is immediately obvious that no simple compromise is available since when delta (δ) is high, nonlinear phase shift will distort the response curve, whereas when delta is low, amplitude amplification will distort the response curve. However, there appears to be little doubt that of the two (phase or amplitude distortion) greater clinical significance is associated with faithful amplitude response than with faithful phase response.

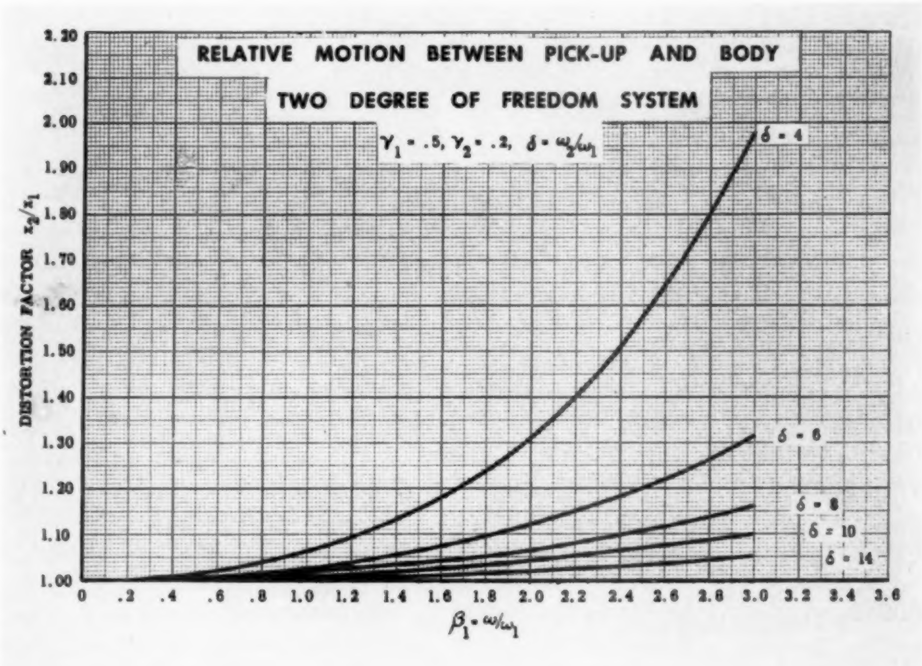

Fig. 7.—Distortion curve for various values of frequency ratio (δ).

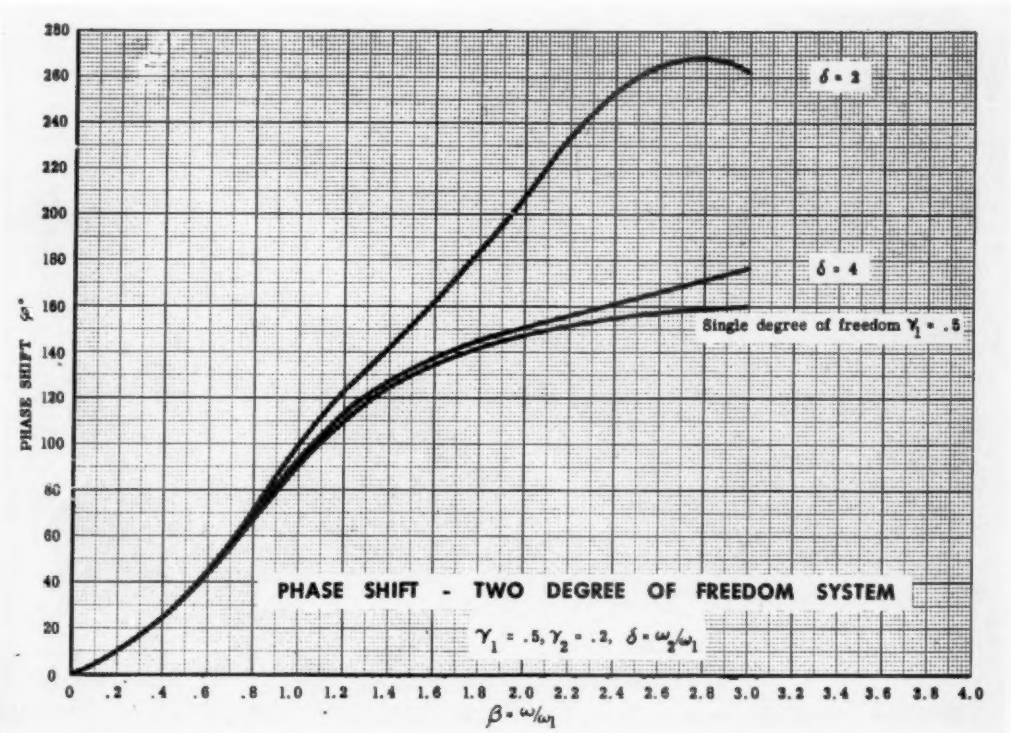

Fig. 8.—Phase-shift curves for frequency ratios of 2 and 4 compared with single degree of freedom with body damping of 0.5 (50 per cent of critical).

DISCUSSION

From the data presented in this paper it is apparent that unless due regard is given to the complete system-instruments, characteristics of the body to which the instruments are coupled, as well as the means of coupling, erroneous results may be obtained when the Dock type ballistocardiograph is employed. It has been shown that by merely adding weight to the platform which rests on the shin bone, an abnormal ballistic record can be modified to the point where it becomes a normal record and vice versa. For any given cardiovascular periodic force the ballistic record is a function of the frequency parameter delta (ratio of pickup frequency to body frequency), natural frequency of the body, body and pickup damping as well as the mass ratio m. Of the parameters listed the two most significant ones affecting the ballistic record are frequency parameter δ and body damping. The frequency parameter δ can be controlled to some extent by the clinician, since the pickup frequency can readily be varied by adjusting the elastic stocking and/or by choosing an appropriate platform weight.

If faithful recording of the body motion per se is desired, it can be seen that ideally, from the distortion curves in Fig. 7, the natural frequency of the pickup should be fourteen times the natural frequency of the body to record all frequency components up to three times the body frequency with less than 5 per cent distortion. It is probable that this is not clinically feasible with the Dock technique. On the other hand, it has been shown, in Figs. 5 and 6, that the body itself amplifies frequency components at and below the natural frequency of the body and attenuates higher frequency components.

If faithful recording of the cardiovascular forces is desired, since the body tends to attenuate the high frequency components, the choice of a pickup frequency which is lower than fourteen times the body frequency will probably yield the best results. At this time, on the basis of our evaluation of the problem, it would appear that for the case of delta of approximately six, on the low frequency end of the significant frequency range, the distortion introduced by the pickup will be insignificant, whereas on the high end of the frequency range, the distortion although significant will be such that it will result in a signal more closely approximating linear response to the input force.

In other words it may be possible to compensate for the attenuation of higher frequencies due to the body per se by a lower frequency in the platform, in order to more closely approximate a linear response for the whole system. Although the effect of attenuation of the high frequency components in the displacement record of the ballistocardiograph may not be readily discernible, it can readily be shown that such attenuation could result in a very marked distortion of the velocity and acceleration records. Since it is now recognized that notches in the acceleration record due to high frequency components have clinical significance in certain cases of heart disease, the importance of faithful response to the input force over the entire range must be considered.

There is no doubt that useful clinical data can be obtained with frequency ratios (pickup to body) lower than 6. In a previous paper, utilizing a three-pound mass on a segment of elastic stocking between the platform and the skin, the platform frequency was maintained at 20 cycles. An analysis of fifty normal

adults between 30 and 40 years of age compared with twenty cases of known coronary heart disease showed results that were clinically useful.

Figure 9 shows the relatively good correlation obtained in this study. Although some overlapping is shown by this study, it should be noted that the degree of overlap is insignificant compared with the results recently reported by other investigators. Some of the overlap may be explained by the fact that no accurate method of determining the natural frequency of the body was available. Thus, although the frequency of the pickup was maintained at 20 cycles, the frequency ratio delta probably varied from 3.7 (if the body frequency was 6 cycles) to 6.7 (if the body frequency was 3 cycles). In the future if a simple method of determining the body frequency is available, the clinician could probably further reduce the scatter in results by adjusting his platform frequency in such a manner as to keep the frequency ratio constant rather than to maintain the pickup frequency at some fixed value.

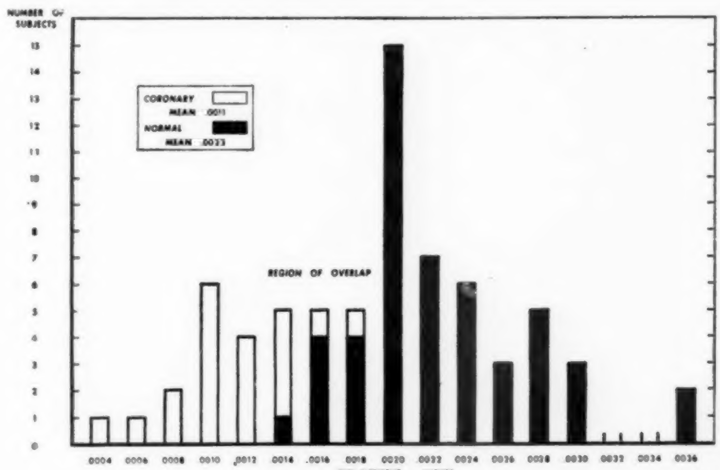

Fig. 9.—Displacement of the body reflected in ballistocardiographic tracings. This chart shows amplitudes of displacement IJ segments in fifty normal persons and twenty cases of healed myocardial infarction in persons between 30 and 40 years of age obtained with platform frequency of approximately 20 cycles. From Smith: Am. Heart J. **46**:692, 1953.

The second significant factor which would account for some of the scatter is that of differences in body damping. From a comparison of the response curves in Figs. 5 and 6*A*, it can readily be seen that if all other variables were held fixed, one could still get appreciable differences in amplitude due to differences in body damping. From preliminary investigations the damping present in the body appears to be a function of age; the older age groups show higher damping coefficients than the younger groups. Until more accurate means of determining body damping become available, it may only be possible to set up ballistic standards by age groups, since within a small age group the probability exists that the variation in body damping from person to person is small. The subject of body damping needs more thorough study. This study should involve large numbers of adults in different age groups.

SUMMARY AND CONCLUSIONS

1. The indiscriminate use of individually calibrated instruments can lead to the same types of errors as those introduced by uncalibrated instruments. To be clinically useful calibrated instrumentation requires an understanding of the operation and limitations of the complete ballistic system.

2. It is recognized that the treatment of the problem of the body and pickup as a two degree of freedom system may be an oversimplification of the more complex system. However, proper consideration of the factors in this simple system has resulted in a marked reduction in scatter of amplitudes in normal individuals from the same age groups.

3. For faithful recording of the motion of the body with a Dock type of pickup, the pickup frequency should be at least fourteen times the frequency of the body. For recording of the cardiovascular forces, a pickup frequency of approximately six times the body frequency appears to yield clinically valid data (although clinically significant data were obtained with a frequency ratio of 4). Further study of the significant frequency components in the cardiovascular forces is needed before an optimum value of pickup frequency can be determined. An analysis of the frequency components of the forcing function (by Fourier analysis) for a large number of abnormal and normal subjects is needed.

4. By means of an elastic stocking and a five-ounce pickup it is possible to maintain a pickup frequency at approximately 35 cycles. By the simple addition of weight to the platform, the natural frequency of the pickup can be lowered and controlled as desired. It can readily be seen that distortion from different body frequencies can be kept small, with a platform frequency of 35 cycles, since a body frequency of 4 would have a delta of approximately 9, whereas, a body frequency of 6 would have a delta of approximately 6. Thus, over a fairly large portion of the frequency range the relative distortion between these two values of delta (6 and 9) is negligible.

5. The problem of the two degree of freedom system may be as important in the table type of ballistocardiograph as in the Dock type. In the ballistic table type of ballistocardiograph the complete system must be treated as a two degree of freedom system in which the first degree of freedom is the body mass with its characteristic damping and natural frequency and the second degree of freedom is represented by the table and its natural frequency and damping. An improper choice of table, the characteristics of which are affected by the mass of the body placed on it, may result in distortion of the signal coming from the pickup to the extent that the data so obtained is meaningless. In the addendum of this paper, it is shown that for the undamped high-frequency table the characteristics of the second degree of freedom are as important as in the Dock type treated here.

ADDENDUM

The Ballistic Table.—In view of recent reports of high incidence of abnormal records for known normal individuals in the age group over 50, as well as reports of high incidence of normal records for known abnormal individuals in the age group under 40, the reports being based on measurements made on high-frequency ballistic tables, a brief investigation of the second degree of freedom for the case of a table was made in order to determine whether the factors covered in this paper would be applicable to the ballistic table. The solution of the equations of motion for the undamped ballistic table was found, and a plot made for the response of the table as a function of impressed frequency. For the cases investigated it was assumed that the weight of the table top was 60 pounds and the natural frequency of the unloaded table was assumed to be 20 cycles and $\delta = 4$. (These values are believed to be approximately the same as those for most high-frequency tables.) Curve (*1*) of Fig. 10 represents the response curve for the case of a 150-pound individual whose body damping value is 0.5 of critical; curve (*2*) is the response curve for $\gamma = 0.5$ for a 200-pound individual; and curve (*3*) is for $\gamma = 0.3$ and w = 150 pounds. From an examination of the curves of Fig. 10, it is obvious that the high-frequency tables in common use today are subject to difficulties similar to those encountered with the Dock type pickup when used on the leg. In all likelihood, the neglect of proper consideration of the second degree of freedom in the case of the table is responsible for the scatter in results obtained on such tables.

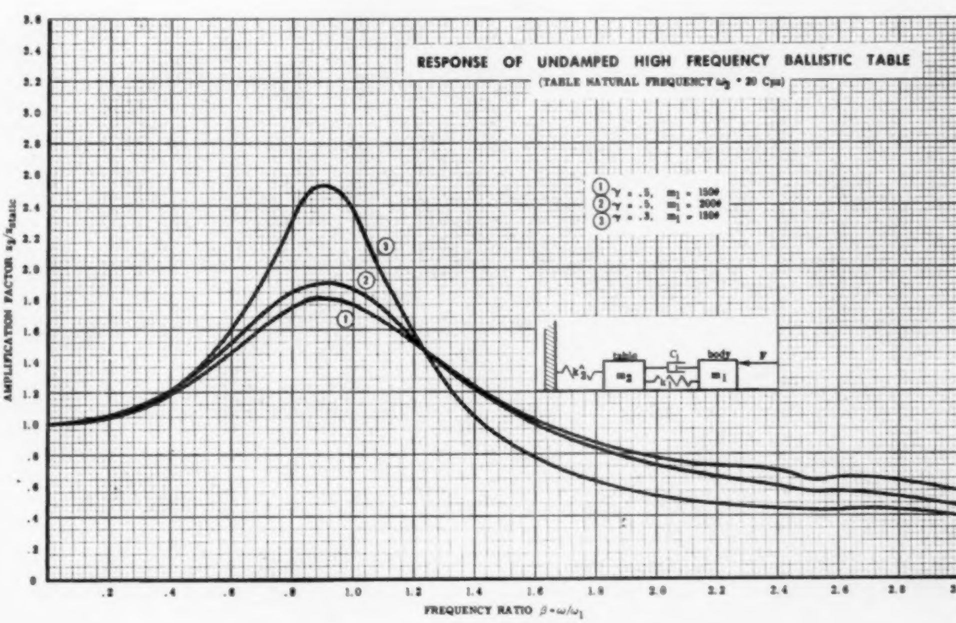

Fig. 10.—Response curve of a high-frequency ballistic table for different values of body weight and body damping. (k_2 refers to spring in the ballistic table.)

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RS-T SEGMENT ELEVATION IN MID- AND LEFT PRECORDIAL LEADS AS A NORMAL VARIANT

MERVIN J. GOLDMAN, M.D.

OAKLAND, CALIF.

ELEVATION of the RS-T segment is a well recognized electrocardiographic finding in many pathologic conditions, such as acute myocardial infarction, acute pericarditis, and ventricular aneurysm. Persistent elevation is also seen in right precordial leads in association with intraventricular block, especially left bundle branch block and left ventricular hypertrophy. Relatively few reports[1,3,5] have appeared regarding RS-T elevation as a normal finding. Myers[6] states that an elevation of the RS-T junction may be considered within normal limits if the displacement does not exceed 2.0 mm. and provided that the RS-T segment immediately begins to rise above the junction in an arc with upward concavity which ends in a tall upright T wave. In a review of fifty-two normal electrocardiograms, S-T elevation of 0.5 mm. to 1.5 mm. occurred in eighteen instances in Leads V_1 through V_6. In one case a 2 mm. elevation occurred in Lead V_2. Wilson[7] illustrates a normal precordial electrocardiogram which is an example of this normal variant. Many cardiologists[2,4] are aware of this phenomenon, but no references have been found which report RS-T elevations of over 2 mm. as a normal variant. Likewise, no reference is known that establishes this phenomenon as occurring more frequently in the Negro race, and there are no reports as to the effect of exercise on this electrocardiographic pattern.

In the past three years twenty-five patients have been seen whose electrocardiograms have shown RS-T segment elevations of 2 to 4 mm. in mid- and left precordial leads (V_3 through V_6). In twenty-three of the twenty-five there was absolutely no clinical evidence of organic heart disease. Some of these patients have been followed for two years with no electrocardiographic change and no evidence of heart disease. Two of the twenty-five did have associated heart disease (one case of "benign" pericarditis and one case of coronary artery disease), but because of the persistence of the RS-T elevations, irrespective of the other electrocardiographic changes and the clinical course, it is concluded that these RS-T changes were in all probability not manifestations of organic heart disease. Admittedly, this latter statement is subject to question.

From the Oakland Veterans Administration Hospital, Oakland, California.

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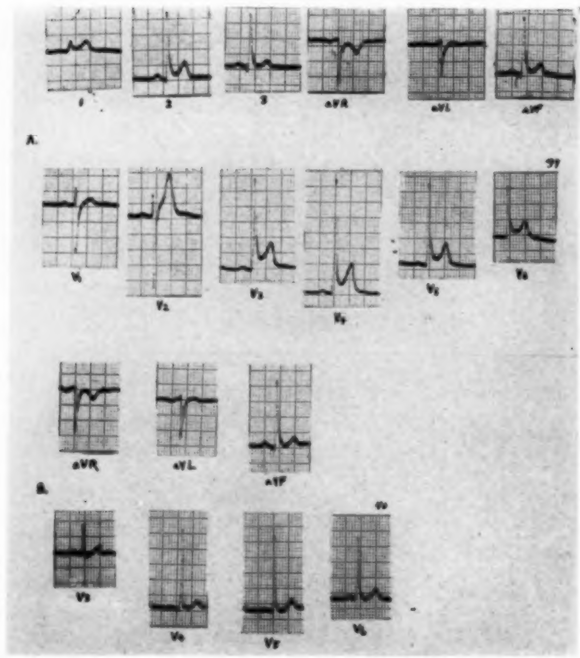

Fig. 1.—Electrocardiograms of a normal 24-year-old Negro. *A.* Taken at rest. Note RS-T elevations in Leads V_2 through V_6. *B.* Taken immediately following exercise. RS-T segments are now isoelectric.

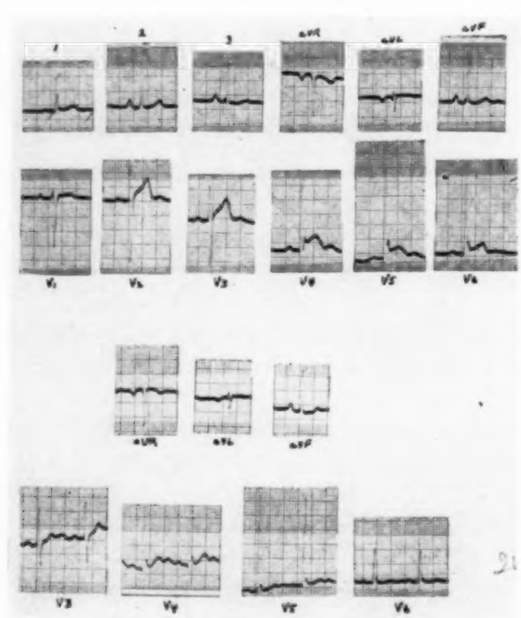

Fig. 2.—Electrocardiograms of a normal 29-year-old Negro. Upper twelve leads were taken at rest; lower nine leads taken immediately following exercise.

Of the twenty-five patients studied, twenty-three were Negroes and nineteen were in the 20 to 34 year age group (see Table I).

TABLE I

AGE	NEGRO	WHITE
20–29	13	
30–34	7†	
35–39	2	
40–49	1	1*
50–59		1
Total	23	2

*Associated coronary artery disease.
†One patient in this group had associated "benign" pericarditis.

All of the twenty-five patients were subjected to the standard Master's exercise test.[8] In every instance the previously elevated RS-T segments returned to the isoelectric line immediately following exercise (see Figs. 1 and 2). Since

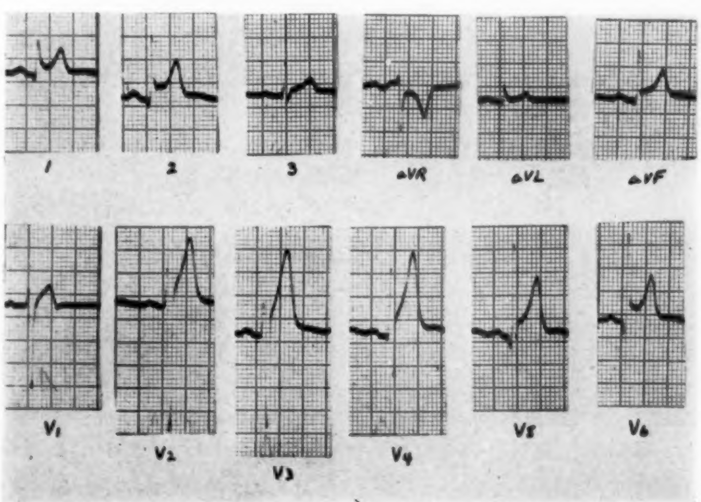

Fig. 3.—Electrocardiogram of a 27-year-old white man with acute "benign" pericarditis. Note similarity to the records in Figs. 1 and 2.

this electrocardiographic pattern of RS-T elevation closely resembles the pattern of acute pericarditis (see Fig. 3), two patients with "benign" pericarditis whose electrocardiograms demonstrated marked RS-T elevations in precordial leads were similarly studied with the Master's test. In neither instance was there any change in the RS-T segment. This latter study was naturally limited due to the hesitancy to perform an exercise test on an individual with active heart disease.

The degree of the RS-T elevation in precordial Leads V_3 through V_6 is shown in Table II. Leads V_1 and V_2 are not included in this study since RS-T elevation n these leads is a normal finding.

TABLE II

	2 MM.*	2½ MM.	3 MM.	3½ MM.	4 MM.
V_3	12†				
V_4	17	4	3	2	2
V_5	13	4	3	2	2
V_6	12	3	3	1	1

*Degree of RS-T elevation.
†Number of cases.

DISCUSSION

From this study it is seen that RS-T segment elevation (2 to 4 mm.) can occur in precordial Leads V_3 through V_6 as a normal variant. This pattern more commonly occurs in young Negroes. From the study of a single electrocardiogram it may be impossible to differentiate this pattern from that of acute pericarditis or recent myocardial infarction. The clinical evaluation of the patient and serial electrocardiographic studies will be necessary to differentiate these conditions. In the absence of all clinical signs of heart disease a Master's exercise test, which results in the return of the elevated RS-T segments to the isoelectric line, will favor the diagnosis of a normal variant.

The mechanism of these electrocardiographic findings cannot be adequately explained. It may be stated that the electromotive forces generated during repolarization have reached sufficient magnitude prior to the termination of depolarization, resulting in the upward displacement of the RS-T junction. After exercise, either the forces of depolarization are accelerated or those of repolarization slowed, resulting in an isoelectric RS-T junction.

SUMMARY

1. Elevation of 2 to 4 mm. of the RS-T segment in Leads V_3 through V_6 may occur as a normal variant.

2. This pattern occurs more commonly in young Negroes.

3. This pattern can be confused with the pattern of acute pericarditis or early myocardial infarction.

4. After exercise the RS-T segment becomes isoelectric.

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THE SPATIAL ANGLE BETWEEN THE LONG AXIS OF THE QRS LOOP AND THE LONGITUDINAL AXIS OF THE VENTRICLES

NOBLE O. FOWLER, JR., M.D.,* AND ROBERT A. HELM, M.D.

CINCINNATI, OHIO

THE positional relationship between the spatial QRS loop and the longitudinal axis of the cardiac ventricles is of interest in studies relating anatomic and electrical heart position. Although the spatial angle between the mean spatial QRS vector ($S\hat{A}_{QRS}$) and the longitudinal axis of the cardiac ventricles (H) has been estimated by Ashman and associates,[1] the relationship has not, to our knowledge, been calculated mathematically. We, therefore, decided to determine the spatial angle, hereafter called θ, between H and the long axis of the QRS loop which is employed instead of the mean QRS vector as a matter of convenience. The derivation of trigonometric formulae for the determination of the spatial angle between two vectors, given the projection of the vectors upon any two of three mutually perpendicular planes, provided the opportunity to calculate this value.

It was believed that such a calculation might be of interest for several reasons. In addition to the magnitude and range of the normal angle, some idea of the relationship between the anatomic and electrical position of the heart could be obtained. Further, the use of more than one system for estimating the long axis of the QRS loop would give a basis for comparison between the different systems. Finally, it was hoped that some information could be obtained with regard to the validity of the lead used for the sagittal component of the spatial vectorcardiogram. For these reasons, the following study was undertaken.

MATERIAL

The subjects used in this study were twenty-five patients from the Medical Clinic and the wards of the Cincinnati General Hospital. An effort was made to obtain approximately equal distribution between the horizontal and vertical electrical positions of the ventricles. All patients had normal scalar electrocardiograms, comprising Leads I, II, III, aV_R, aV_L, aV_F, and V_1 to V_6.

From the Cardiac Laboratory, Cincinnati General Hospital, and the Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

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*Present address: Cardiac Laboratory, The Brooklyn Hospital, DeKalb Avenue & Ashland Place, Brooklyn 1, New York.

METHOD

The spatial longitudinal axis of the ventricles was estimated as follows. Seven-foot teleroentgenograms of the chest were made in two positions: supine anteroposterior and supine left lateral. Upon the anteroposterior teleroentgenogram a straight line was drawn from the junction of the lower border of the right pulmonary artery with the great vessels to the junction of the cardiac apex and the diaphragm. The angle ($\alpha\, x\, y$, Fig. 1) between the horizontal axis (x) and this line was then measured in a clockwise manner. Upon the lateral teleroentgenogram a straight line was drawn from the hilar shadow to the cardiac apex. The angle ($\alpha\, y\, z$, Fig. 1) between the vertical axis (Y) and this line was then measured in a clockwise manner, as observed from the right side of the erect

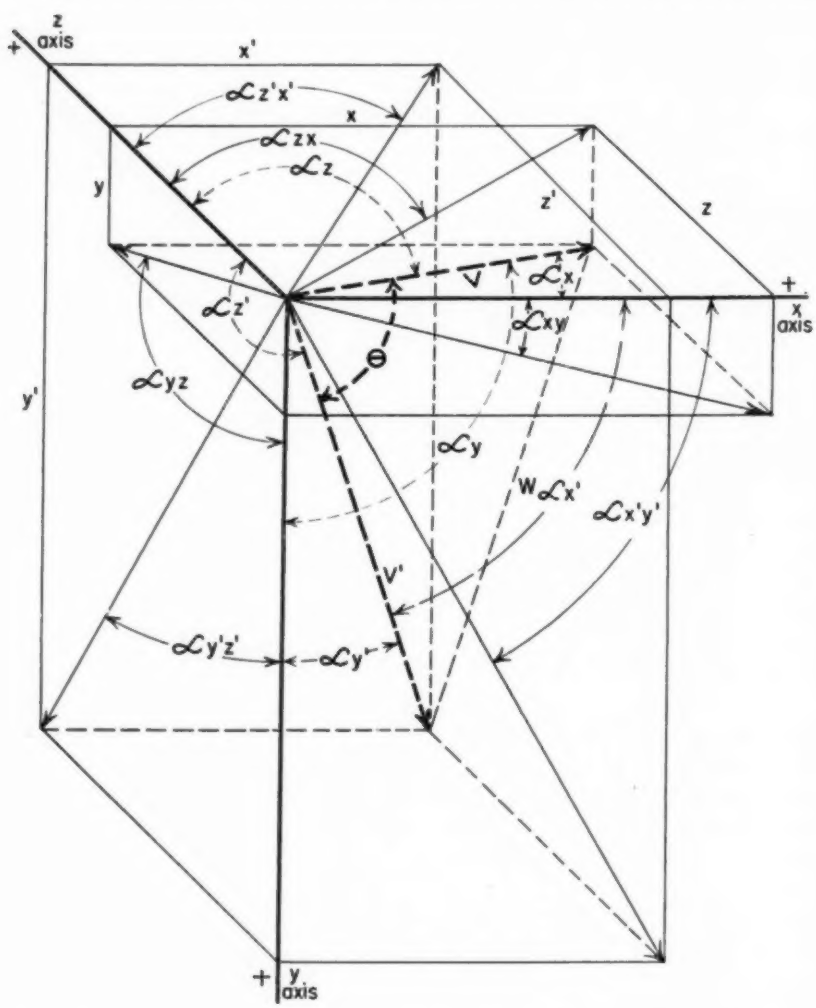

Fig. 1.—Diagram illustrating the designations of the angular measurements. See text. From Helm and Fowler: Am. Heart J. **46**:231, 1953, (Fig. 1).

subject. Figure 1 contains a Cartesian coordinate system of three mutually perpendicular axes, x (horizontal), y (vertical), and z (anteroposterior). If the spatial anatomic axis of the ventricles is represented by V, then the measured frontal plane angle is represented by $\alpha\, x\, y$ and the measured sagittal plane angle by $\alpha\, y\, z$.

Frontal, sagittal, and transverse plane projections of the spatial QRS loops were made with the Technicon Triagram Electrocardiograph and Vectorscope. The vectorcardiograms were recorded by the cube reference system of Grishman and associates[2] and by the equilateral tetrahedron system employed by Burch and coworkers.[3] In the cube system, equal standardization was employed for the horizontal, vertical, and anteroposterior components. In the equilateral tetrahedron system, standardization factors of 1.7 for VF and 1.2 for VB were employed. The direction of inscription of the QRS loop was indicated by a Dumont electronic switch and square-wave generator modified by a capacitor. The spatial loops were photographed upon 35 mm. film and enlarged by projection. The projections of the spatial loop upon each of the three planes were photographed in rapid succession rather than simultaneously. Frontal plane loops were recorded as if looking toward the front of the erect subject. Sagittal plane loops were recorded as if looking toward the right side of the erect subject. Transverse plane loops were recorded as if looking toward the prone subject in a head-to-foot direction. The long axis of the QRS loop was drawn from the origin of the loop to its most distal point. In some instances, satisfactory long axes could not be drawn, and the loops were discarded. The long axes of the QRS loops were used rather than the mean QRS vector. In the frontal plane, an angle ($\alpha\, x'y'$) was measured in a clockwise manner from the subject's left end of the x axis to the QRS axis. In the sagittal plane, an angle ($\alpha\, y'z'$) was measured in a clockwise manner from the inferior end of the y axis to the QRS axis. In the transverse plane, an angle, ($\alpha\, z'x'$) was measured from the posterior end of the z axis in a clockwise manner to the QRS axis.

With reference to Fig. 1, if V' represents the long axis of the spatial QRS loop, then the frontal, sagittal, and transverse projections of V' make angles with the transverse axis (x), the vertical axis (y), and the anteroposterior axis (z), which may be called $\alpha\, x'y'$, $\alpha\, y'z'$ and $\alpha\, z'x'$, respectively.

The spatial angle, θ, between the anatomic long axis of the ventricles, V, and the long axis of the QRS loop, V', may be calculated as follows. (Complete derivation of these formulas is given in another paper.)[4]

$$\text{Cos } \theta = \cos \alpha\, x \cos \alpha\, x' + \cos \alpha\, y \cos \alpha\, y' + \cos \alpha\, z \cos \alpha\, z'$$

$$\begin{aligned}
\cot \alpha\, x &= (\cot \alpha\, xy)\ (\cos \alpha\, yz) \\
\cot \alpha\, x' &= (\cot \alpha\, x'y')\ (\cos \alpha\, y'z') \\
\cot \alpha\, z &= (\tan \alpha\, yz)\ (\sin \alpha\, xy) \\
\cot \alpha\, z' &= (\tan \alpha\, y'z')\ (\sin \alpha\, x'y') \\
\cos \alpha\, y &= (\cos \alpha\, yz)\ (\sin \alpha\, x) \\
\cos \alpha\, y' &= (\cos \alpha\, y'z')\ (\sin \alpha\, x')
\end{aligned}$$

In some instances, the long axes of the QRS loops could be measured satisfactorily in only two of the three planes. When this occurred, the direction of the long axis of the QRS loop in the third plane could be calculated from the following relationships.

$$\cot \alpha\, zx = \tan \alpha\, xy \ \tan \alpha\, yz$$
$$\cot \alpha\, xy = \tan \alpha\, yz \ \tan \alpha\, zx$$
$$\cot \alpha\, yz = \tan \alpha\, zx \ \tan \alpha\, xy$$

The mean QRS vector in the frontal and transverse planes was also estimated by a modification of the method of Grant.[5] Details of this method are given in another paper.[4] A standard twelve-lead electrocardiogram was made with the Sanborn Viso-Cardiette. Leads I, II, III, aV_R, aV_L, and aV_F were used in determining the direction of the frontal plane mean QRS vector. Leads V_1 to V_6 were used to estimate the direction of the mean QRS vector in the transverse plane. The mean QRS vector was considered to be perpendicular to the transitional zone in either plane and to point in the direction of the largest QRS complexes. The direction of the sagittal plane mean QRS vector was calculated by appropriate formulas from those given here. This method will be referred to hereafter as the VECG (vector electrocardiographic) method. It is realized that some error is involved in comparing the mean QRS vector estimated by this method with the long axis of the QRS loop estimated by the cube and tetrahedron reference systems. However it is believed that the relationship should be sufficiently close to make the comparison of interest.

RESULTS

The results are depicted in Tables I through IV. Table I lists the observed frontal and sagittal projections of the anatomic axis and the corresponding projections of the long axis of the QRS loop observed or calculated with each reference system. Table II lists the values found for angle θxy (frontal projection of θ) and angles θyz (sagittal projection of θ) when measured or calculated by the cube, tetrahedron, and VECG methods. Table III lists the values of θ obtained by each of the three methods. Table IV is a statistical table. It may be seen in Table IV that the mean values of θ by the three systems (tetrahedron = 46.6°; VECG = 59.2°; cube = 50°) were not significantly different ($p = > 0.2$; > 0.1; > 0.7). It may also be noted that the mean values of θ were significantly different from zero ($p = < 0.01$) and from 90° ($p = < 0.01$) by all three methods. Graphing of the values of θ against their expected deviation by the rankit method indicated by their failure to form a straight line that the values of θ were not normally distributed and thus could not be used to determine a correlation coefficient. The logarithmic values of θ were also not normally distributed. The relationships between θ, θxy, and θyz as determined by the three methods were therefore studied by means of the regression coefficient, byx.[6] As may be seen in Table IV a significant relationship was found between the tetrahedron and VECG systems insofar as the values of θ were concerned. The regressions between VECG and cube and between cube and tetrahedron were not significant for θ.

TABLE I. FRONTAL AND SAGITTAL PROJECTIONS OF THE LONGITUDINAL AXIS OF THE HEART AND OF S$\hat{A}_{QRS}$

SUBJECT NO.	FRONTAL PLANE				SAGITTAL PLANE			
	ANATOMIC (α xy) DEGREES	CUBE (α x'y') DEGREES	TETRAHEDRON (α x'y') DEGREES	VECG (α x'y') DEGREES	ANATOMIC (α yz) DEGREES	CUBE (α y'z') DEGREES	TETRAHEDRON (α y'z') DEGREES	VECG (α y'z') DEGREES
1	51	61	—	75	312	358	—	375
2	35	15	25	15	323	425	415	393
3	30	22	61	70	303	358	349	380
4	38	24	—	−5	309	386	—	456
5	45	−30	−81	−40	318	155	151	495
6	37	15	—	10	298	349	—	429
7	45	41	83	75	320	357	347	371
8	31	−6	−29	−15	314	478	156	480
9	44	59	—	80	324	365	—	368
10	26	25	—	35	298	371	—	387
11	35	26	19	25	318	378	313	411
12	38	38	25	35	303	334	343	344
13	30	20	−9	5	315	388	146	439
14	37	18	30	30	320	401	345	392
15	52	8	—	45	316	323	—	365
16	36	18	62	50	329	400	353	395
17	48	49	81	65	313	366	356	362
18	33	56	—	90	322	351	—	360
19	34	24	—	−30	307	371	—	130
20	32	—	12	20	301	—	317	374
21	32	17	10	20	313	403	382	386
22	37	34	52	50	313	364	364	377

Frontal plane angles are measured clockwise from the patient's left end of the horizontal axis. Sagittal plane angles are measured clockwise from the inferior end of the vertical axis.

When α y'z' exceeds 360°, it indicates that 360° were added to the original measurement to make θyz as small as possible.

The mean values of θxy were −12.14° (cube); −5.27° (VECG); and −17.42° (tetrahedron). These values were not significantly different from each other or from zero in the tetrahedron and VECG systems but were significantly different from zero in the cube system. Regressions (Table IV) showed highly significant associations between the three methods for values of θxy. The mean values of θyz were 67.76° (cube); 88.09° (VECG); and 66.68° (tetrahedron). These values were not significantly different from each other, but were significantly different from zero (Table IV). Regressions showed highly significant associations between the three methods for values of θyz.

Regressions were also made between the values of $\alpha\ xy$ and $\alpha\ x'y'$ by the three systems (Table IV). No significant association was found. In like manner regressions were set up for $\alpha\ yz$ and $\alpha\ y'z'$ by the three systems. The only significant regression was for the values of $\alpha\ yz$ determined by the VECG system.

TABLE II. FRONTAL AND SAGITTAL PROJECTIONS OF THE SPATIAL ANGLE BETWEEN $\hat{SA}_{QRS}$ AND THE LONGITUDINAL AXIS OF THE HEART

SUBJECT NO.	θXY (FRONTAL) (DEGREES)			θYZ (SAGITTAL) (DEGREES)		
	CUBE	TETRAHEDRON	VECG	CUBE	TETRAHEDRON	VECG
1	10	—	24	46	—	63
2	−20	−10	−20	103	92	70
3	−8	31	40	56	46	77
4	−14	—	−43	77	—	147
5	−75	−126	−85	163	167	177
6	−22	—	−27	51	—	131
7	−4	38	30	37	27	51
8	−37	−60	−46	164	158	166
9	15	—	36	41	—	44
10	−1	—	9	73	—	89
11	−9	−16	−10	60	5	93
12	0	−13	−3	31	40	41
13	−10	−39	−25	73	169	124
14	−19	−7	−7	81	25	72
15	−44	—	−7	7	—	49
16	−18	26	14	71	24	66
17	2	33	17	53	43	49
18	23	—	57	29	—	38
19	−10	—	−64	64	—	177
20	—	−20	−12	—	16	73
21	−15	−22	−12	90	69	73
22	−3	15	13	51	51	64
Mean	−12.14	−17.42	−5.27	67.76	66.68	88.09

Angles are measured clockwise from the anatomic axis.

TABLE III. CALCULATED SPATIAL ANGLES BETWEEN $\hat{SA}_{QRS}$ AND THE ANATOMIC AXIS OF THE HEART (Θ)

SUBJECT NO.	VECG (DEGREES)	CUBE (DEGREES)	TETRAHEDRON VECG (DEGREES)
1	60	42	—
2	39	56	56
3	68	38	40
4	86	50	—
5	103	85	134
6	76	49	—
7	50	29	39
8	68	53	71
9	49	34	—
10	56	44	—
11	56	37	17
12	35	27	38
13	56	38	49
14	45	117	20
15	82	117	—
16	50	39	29
17	43	43	46
18	42	27	—
19	90	42	—
20	48	—	35
21	41	47	40
22	48	35	39
Mean	59.2	50.0	46.6

By means of Fisher's z test,[7] the variances from regression of VECG θyz on tetrahedron θyz and of cube θyz on tetrahedron θyz were compared. Although the variance from regression was much greater in the case of cube θyz on tetrahedron θyz, the difference was not significant statistically

$$\left(\frac{S_2^2}{S_1^2} = 2.35;\ p = >0.05\right).$$

TABLE IV. STATISTICAL SUMMARY

CALCULATION	VALUE OF b_{yx}	VALUE OF t	VALUE OF p
1. Standard error of means, VECG and Cube Θ's		1.28	>0.2
2. Standard error of means, VECG and Tetrahedron Θ's		1.55	>0.1
3. Standard error of means, Cube and Tetrahedron Θ's		0.37	>0.7
4. Standard error of means, VECG and Cube angle Θxy		0.807	>0.4
5. Standard error of means, VECG and Tetrahedron Θxy		0.906	>0.3
6. Standard error of means, Cube and Tetrahedron Θxy		0.4949	>0.6
7. Standard error of means, VECG and Cube angle Θyz		1.58	>0.1
8. Standard error of means, VECG and Tetrahedron Θyz		1.12	>0.2
9. Standard error of means, Cube and Tetrahedron Θyz		0.06	>0.9
10. Difference from zero, mean VECG Θ		14.88	<0.01
11. Difference from 90°, mean VECG Θ		7.9	<0.01
12. Difference from zero, mean Tetrahedron Θ		6.1	<0.01
13. Difference from 90°, mean Tetrahedron Θ		5.7	<0.01
14. Difference from zero, mean Cube Θ		8.99	<0.01
15. Difference from 90°, mean Cube Θ		7.2	<0.01
16. Difference from zero, mean VECG Θxy		−0.7124	>0.4
17. Difference from zero, mean Cube Θxy		−2.618	<0.02
18. Difference from zero, mean Tetrahedron Θxy		−1.562	>0.1
19. Difference from zero, mean VECG Θyz		9.19	<0.01
20. Difference from zero, mean Cube Θyz		8.02	<0.01
21. Difference from zero, mean Tetrahedron Θyz		4.34	<0.01
22. Regression, VECG Θ on Cube Θ	0.26	1.63	>0.8
23. Regression, Tetrahedron Θ on Cube Θ	0.34	1.00	>0.9
24. Regression, VECG Θ on Tetrahedron Θ	0.48	4.36	<0.01
25. Regression, frontal plane, VECG Θxy on Cube Θxy	1.2605	4.359	<0.01
26. Regression, frontal plane, VECG Θxy on Tetrahedron Θxy	0.7113	15.179	<0.01
27. Regression, frontal plane, Tetrahedron Θxy on Cube Θxy	1.9099	5.528	<0.01
28. Regression, sagittal plane, Cube Θyz on Tetrahedron Θyz	1.03	3.68	<0.01
29. Regression, sagittal plane, VECG Θyz on Cube Θyz	0.81	4.05	<0.01
30. Regression, sagittal plane, VECG Θyz on Tetrahedron Θyz	0.59	4.92	<0.01
31. Regression, frontal plane, Cube α xy on α x′y′	0.6166	0.9168	>0.3
32. Regression, frontal plane, Tetrahedron α xy on α x′y′	1.4846	0.6863	>0.5
33. Regression, frontal plane, VECG α xy on α x′y′	1.4291	1.3111	>0.2
34. Regression, sagittal plane, cube α yz on α y′z′	0.4840	0.3027	>0.7
35. Regression, sagittal plane, Tetrahedron α yz on α y′z′	0.2197	0.0676	>0.9
36. Regression, sagittal plane, VECG α yz on α y′z′	6.35	5.7846	<0.01

DISCUSSION

Ashman and associates[1] estimated that the spatial angle between $S\hat{A}_{QRS}$ and H approximated 90°. Our angles were somewhat smaller than this on the average, a significantly smaller angle being found by each of the three methods employed. The discrepancy may be due to the fact that in two of three methods employed, we measured the long axis of the QRS loop rather than the mean QRS vector. Although this increases the variation between the two methods, it is felt that a difference of this magnitude between the long axis of the QRS loop and the mean QRS vector would probably not be observed in normal persons. Ashman and associates[1] found $S\hat{A}_{QRS}$ to lie posterior to H. We found the long axis of the QRS loop to lie also posterior to H in all cases studied and by all three methods of measurement. In the frontal plane, however, the long axis of the QRS loop was found to be either superior or inferior to H, being inferior more often than superior by all three systems.

The large range in normal variation of angles θxy and θyz would indicate difficulty in the estimation of the anatomic position of the ventricles from the position of the QRS axis. The much smaller mean size of θxy, which was in fact not significantly different from zero in the VECG and tetrahedron systems, suggests that such estimation is more likely to be accurate in the frontal than in the sagittal planes. This same conclusion was reached in a previous study.[8] However, the failure to find regression of significance between the angular positions of the anatomic axis of the ventricles and the long axis of the QRS loop in the frontal plane implies considerable difficulty in the frontal plane as well.

Unfortunately, the data shed little light upon which of the three systems employed is the most accurate. It is apparent that there are some significant differences in the three systems. Although the mean values of θ, θxy, and θyz were not significantly different when determined by the three different systems, significant regression for θ was found only in one of three paired systems. Since significant associations between H and the long axis of the QRS loop were not found in the frontal plane in any of the three systems and were found in the sagittal plane only by the VECG system; no comparison between the systems can be made for accuracy. The VECG system appears to be as satisfactory as the other two for determining the general direction of the QRS loop. Here again we must realize that there is some error in comparing the mean QRS axis as determined by VECG with the long axis of the QRS loop measured by the two other methods.

For the same reasons, since significant association between the long axis of the QRS loop and H was not found in the frontal plane and was found in the sagittal plane only by the VECG system, no statement can be made with regard to the relative accuracy of frontal and sagittal plane projections of the spatial QRS loop.

SUMMARY AND CONCLUSIONS

1. An estimation of the spatial angle (θ) between H and the long axis of the QRS loop was made. H was determined from chest teleroentgenograms. The position of the QRS loop was studied by three methods: (1) by a modification of the method of Grant (VECG); (2) from plane projections of the spatial QRS loop recorded from a cube reference frame; (3) from projections of the spatial QRS loop recorded from an equilateral tetrahedron reference frame.

2. The mean values of θ were 50° (cube); 46.6° (tetrahedron); 59.2° (VECG).

3. Although the mean values of θ and its frontal and sagittal projections were not significantly different when determined by the three systems, significant association between the systems for values of θ was not always found.

4. Failure to find significant association between the position of H and the QRS loop suggests difficulty in predicting the anatomic heart position from the long axis of the QRS loop.

5. No conclusion could be reached with regard to the relative accuracy of the three methods of estimating the QRS loop position or with regard to the relative accuracy of frontal and sagittal plane projections of the long axis of the QRS loop. No evidence was found to indicate that the VECG method of estimating QRS loop position is less accurate than the other two methods employed. This applies only to the axis of the loop and does not imply that routine nonsimultaneous precordial leads may be used to derive a spatial QRS loop.

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SEQUENTIAL ELECTROCARDIOGRAPHIC CHANGES FOLLOWING AURICULAR INJURY

Thomas N. James, M.D., and Thomas Geoghegan, M.D.

Detroit, Mich.

INFORMATION regarding the auricular electrocardiographic component is impressively meager when compared to the available data on the ventricular component. Although the majority of auricular electrocardiographic investigations have pertained to fibrillation, flutter, and other arrhythmias,[1-4] an excellent study of the clinical and pathologic, as well as the experimental, features of auricular infarction was made by Cushing and associates[5] in 1942. Other less extensive studies have been made,[6,7] but all were prior to the widespread use of the Wilson indifferent electrode and the Goldberger augmented unipolar extremity leads. On the other hand there have been several clinical reports of auricular infarction in human beings recorded by some of the newer electrocardiographic methods.[8-10]

The paucity of electrocardiographic data on auricular injury patterns has been due to the lack of a reproducibly specific method of producing an experimental injury, the variability of the auricular electrocardiographic response to injury, and the technical problem of recording a tracing which can be definitively interpreted. Additionally, the intermittency of the recordings made in such experiments has left important transient and changing data unpublished. Enlarging upon these facts, Cushing and co-workers[5] found ten totally different electrocardiographic responses to experimentally induced auricular injury, most of which were conduction disturbances. None of the responses was consistent, and the more specific changes were the least encountered.

One would expect a reproducibly specific method of experimental auricular injury to permit the development of a characteristic electrocardiographic pattern. Although thermal[6] and chemical[5] cauterization, intramural injection of alcohol,[7] and ligation of the auricular arteries[5] have been attempted, each method has failed to be sufficiently reproducible. Ligation of the auricular arteries, which is reasonably analogous to human auricular infarction, would seem logical. The anatomic variability of these minute vessels, and the technical difficulty of ligating them, as well as the possible tissue oxygenation from the blood within the auricular chambers, renders this approach of questionable value. Cushing and co-workers[5] have suggested poorer oxygenation from right (venous) intra-auricular blood as the explanation for the higher incidence of right auricular infarction among autopsied hearts.

From the Divisions of Cardiology and General Surgery, Henry Ford Hospital, Detroit, Mich.
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The low voltage of the auricular complex in indirect electrocardiograms has made interpretation tedious and unreliable. The use of semidirect auricular leads from an esophageal electrode[7] partly solves this problem, but this approach has the disadvantage of a fixed electrode which allows no exploration of the auricular surface. Direct auricular electrocardiography has been employed extensively in the study of experimental auricular arrhythmias and in the evaluation of the normal auricular complex.[1-3] Such an approach has been applied to human beings via cardiac catheterization,[11,12] via a thoracoscope,[4] and during thoracotomy.[13,14] To our knowledge direct auricular electrocardiography has not been previously employed in a study of auricular injury.

Our investigation was undertaken to provide some consistent data regarding the effect of auricular injury on the electrocardiogram. We have employed an original method of producing auricular injury, and in addition have used direct auricular leads with continuous recording of the electrocardiogram.

DISCUSSION OF METHODS

For the production of auricular* injury we chose the injection of air into the left ventricular cavity. In a previous study on the effect of air entering the left side of the heart,[15] we confirmed the findings of others[17-19] that the mechanism of death in such a situation is the occlusion of the entire coronary arterial tree by bubbles of the injected air. It was also established that with proper treatment this condition was entirely reversible, including the electrocardiographic changes.[16] Although cardiac function in the untreated dog fails so rapidly that the animal is for practical purposes dead within a few minutes after injection of such air, the heart continues to beat for a much longer period. In this situation the auricles often continued beating after ventricles had ceased, in some cases for well over an hour.

There are numerous advantages to this method of producing auricular injury. They are as follows:

1. Instantaneous occlusion of all the arterial blood supply of the auricles can be achieved simply, with minimal manipulation of the heart and subsequently little trauma.

2. Previous approaches to this problem have usually necessitated the production of auriculoventricular block to isolate the auricular complexes. Our method produces such graphic changes that the production of block is unnecessary.

3. Simultaneous production of ventricular and auricular injury permits study of a state simulating the human cardiac accident. In a review of thirty-one cases of infarction of human auricles at autopsy, Cushing and co-workers[5] found only five in which the ventricles were not also involved.

4. Since a significant portion of auricular oxygenation may be derived from intra-auricular blood, arrest of this blood flow seems desirable: Air injection accomplishes this (via rapid myocardial failure) without producing extensive ventricular dilatation and subsequent injury to the cardiac conduction system.

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*Auricle, as used in this report, is the same structure as the Basle Nomina Anatomica term atrium, denoting the chamber of the heart which first receives venous blood. Auricular appendage refers to the same structure as the Basle Nomina Anatomica term auricle.

Direct leads from various points on the surface of the auricles were obtained by means of an exploring electrode (a piece of saline-soaked cotton tied to the end of the ordinary precordial cable) used through the V terminal of the electrocardiograph. The four points most often recorded (Fig. 1) were a point midway between the entrance of the superior and inferior venae cavae on the right auricle, the sulcus terminalis, a point near the middle of the interauricular septal groove, and a mid-point on the lateral surface of the left auricle. Beginning just before the injection of air, a continuous direct-writer electrocardiogram was made from the position between the venae cavae. From time to time the electrode selector switch was quickly moved to the aV_F or standard Lead II positions without stopping the electrocardiograph motor, thus losing less than one second in the continuous recording.

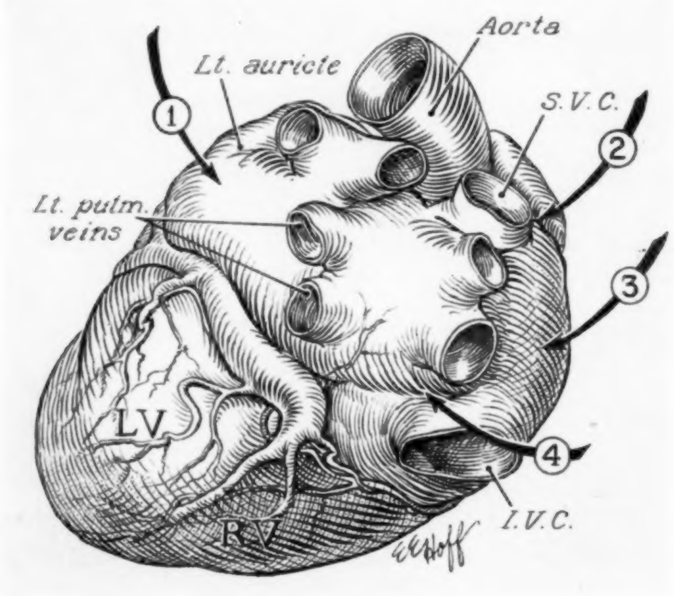

Fig. 1.—Diagram of superior posterior aspect of the heart. Arrows indicate the four positions used in direct auricular exploration. (*1*) Lateral surface of left auricle. (*2*) Sulcus terminalis. (*3*) Midway between superior and inferior venae cavae. (*4*) Interauricular septal groove.

DESCRIPTION OF EXPERIMENTS

The data in this investigation were obtained from five mongrel dogs. With the animals in a supine position a thoracotomy was performed via a transverse incision at the level of the fourth ribs. This permitted free visualization of both auricles. Anesthesia was administered by intermittent positive pressure ether-oxygen. The amount of air injected instantaneously into the left ventricular cavity was 1.5 c.c. per kilogram, a dose we have found to be uniformly lethal. The technique for injection has been described in a previous report.[15] No attempt was made to resuscitate these animals.

Control electrocardiograms were made prior to the injection of air. Recordings were continued until there was no further electrical activity of the heart.

RESULTS

Description of Normal Patterns.—Except for slight variation in position (or axis) of the heart, our control standard and unipolar extremity leads were analogous to those in the human being (Fig. 2). The direct auricular control leads had the following characteristics (Fig. 2, A to D). Both at the sulcus terminalis and midway between the entrance of the cavae into the right auricle, the P waves were predominantly negative with sharp intrinsic deflections. This is as would be expected, since the electrode in these two positions was near the sinoauricular

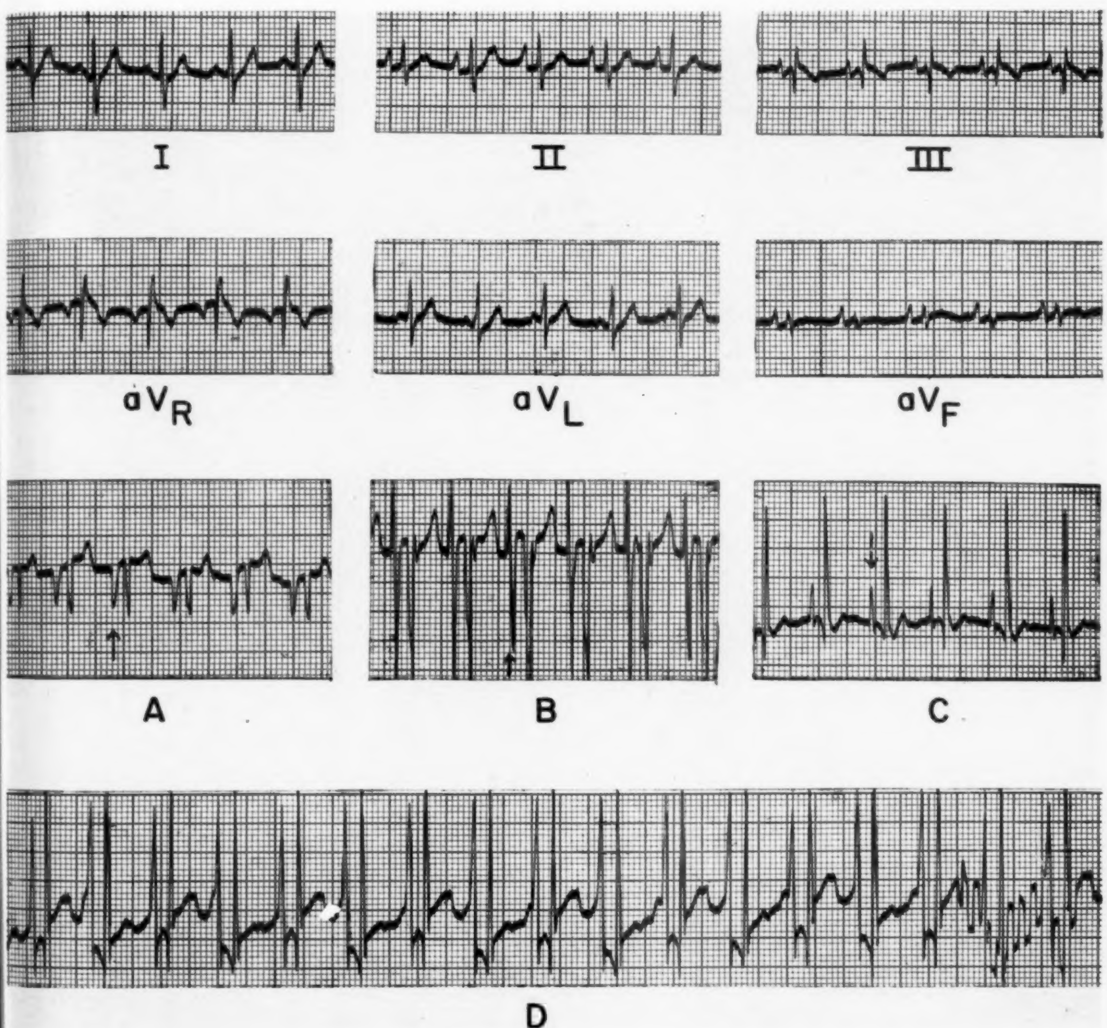

Fig. 2.—Control electrocardiograms. Arrows indicate representative P waves. *A.* Direct right auricular lead. *B.* Direct lead from the interauricular septal groove; note slight P-T_a segment elevation due to light pressure from the electrode. *C.* Direct left auricular lead. *D.* Direct left auricular lead from another animal; note marked P-T_a depression with normal S-T segment, caused by heavy pressure from the exploring electrode.

node and the spread of the auricular excitation wave was almost entirely away from the electrode. At the position on the interauricular septal groove the P wave was plus-minus diphasic, since the auricular excitation wave approached the electrode approximately one-half the time and receded during the second half. Contour of the P wave on the left auricle varied considerably with position, being diphasic on the body of the auricle and predominantly a positive complex on the left auricular appendage, the last area of auricular myocardium activated.[13]

Onset of Injury Patterns.—In a previous electrocardiographic study of the effect of air in the left side of the heart,[16] we found evidence of ventricular injury in the extremity leads within twenty seconds after the injection of air. Auricular injury patterns were much later in appearing in the extremity leads.

Direct auricular leads demonstrated that electrocardiographic evidence of auricular injury appeared simultaneously with that of ventricular injury (Fig. 3). In four of the five dogs auricular and ventricular injury patterns were apparent within 30 seconds after air injection. The fifth dog was given pure oxygen to breathe for one minute prior to injection of intraventricular air, and the onset of injury patterns in this dog was delayed until 45 seconds after air injection.

Types of Injury Patterns.—There was striking consistency in the evolution of typical ventricular and auricular injury patterns. The ventricular patterns were the same as those of acute infarction and have been previously described.[16,18] The auricular injury patterns were of a sufficiently marked degree so that the normal proximity of the QRS did not impair interpretation of changes in the auricular complexes. Furthermore, within one to four minutes, increasing degrees of auriculoventricular block made interpretation even simpler.

The first change of injury in the auricular complex from leads on the right auricle (predominantly negative P wave) was a progressive and striking elevation of the P-T_a segment (Figs. 3, 6, D to G), occurring simultaneously with a similar elevation of the ventricular S-T segment. This was a constant and sequential finding in all five dogs. In direct auricular leads with predominantly positive P waves, this initial injury pattern was a marked P-T_a depression (Fig. 2,D). These changes were not apparent in the extremity leads this early, usually becoming visible only after there was some degree of auriculoventricular block with isolated P waves.

Following a variable duration of P-T_a segment displacement, there occurred another consistent change. This was a transformation of the displaced P-T_a segment into a sharp auricular T wave, whose polarity was opposite to that of the P wave. Thus, in right auricular leads the auricular T wave was a sharp positive deflection (Figs. 3; 4,A; 5,F; 6,A to G), while in left auricular leads it was negative (Fig. 6,I).

An elevated P-T_a segment identical to that obtained from auricular ischemia can also be obtained by pressing the exploring auricular electrode against the auricular epicardium (Fig. 2, B, D). This has been demonstrated by others in auricular[3] as well as direct ventricular leads.[20] When the P-T_a displacement was due to such pressure, there was no concomitant displacement of the S-T segment, and there was no evolution to a sharp auricular T wave.

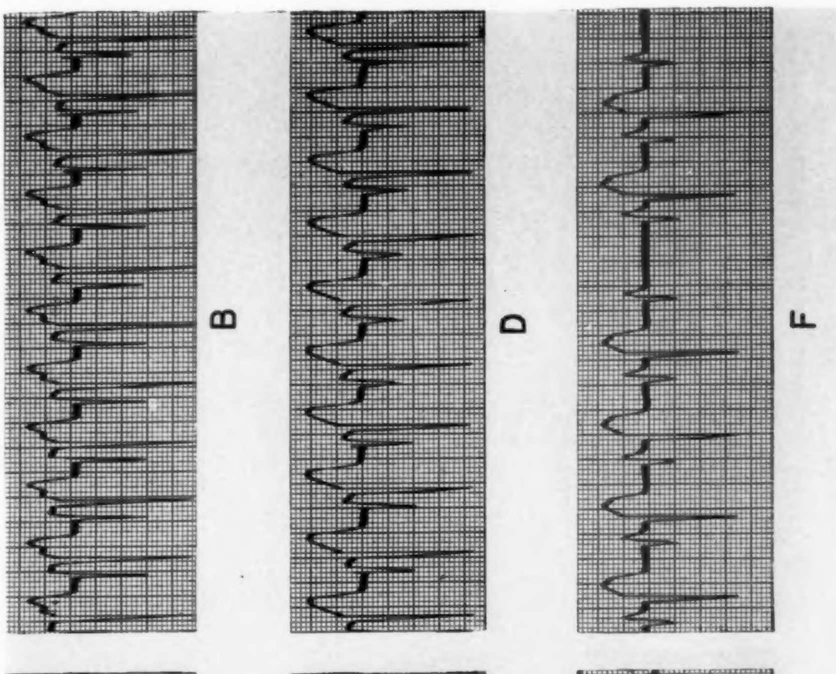

Fig. 3.—Demonstration of simultaneous onset of P-T_a and S-T segment elevation, with evolution of the P-T_a elevation into a sharp auricular T wave. Representative segments of a continuous tracing from the right auricle of dog No. 3. *A.* 45 seconds after air injection. *B.* 1 minute. *C.* 2 minutes. *D.* 2½ minutes. *E.* 3 minutes. *F.* 3¼ minutes. The sharp auricular T wave is best seen in *E* and *F*, with incomplete auriculoventricular block appearing in *F*.

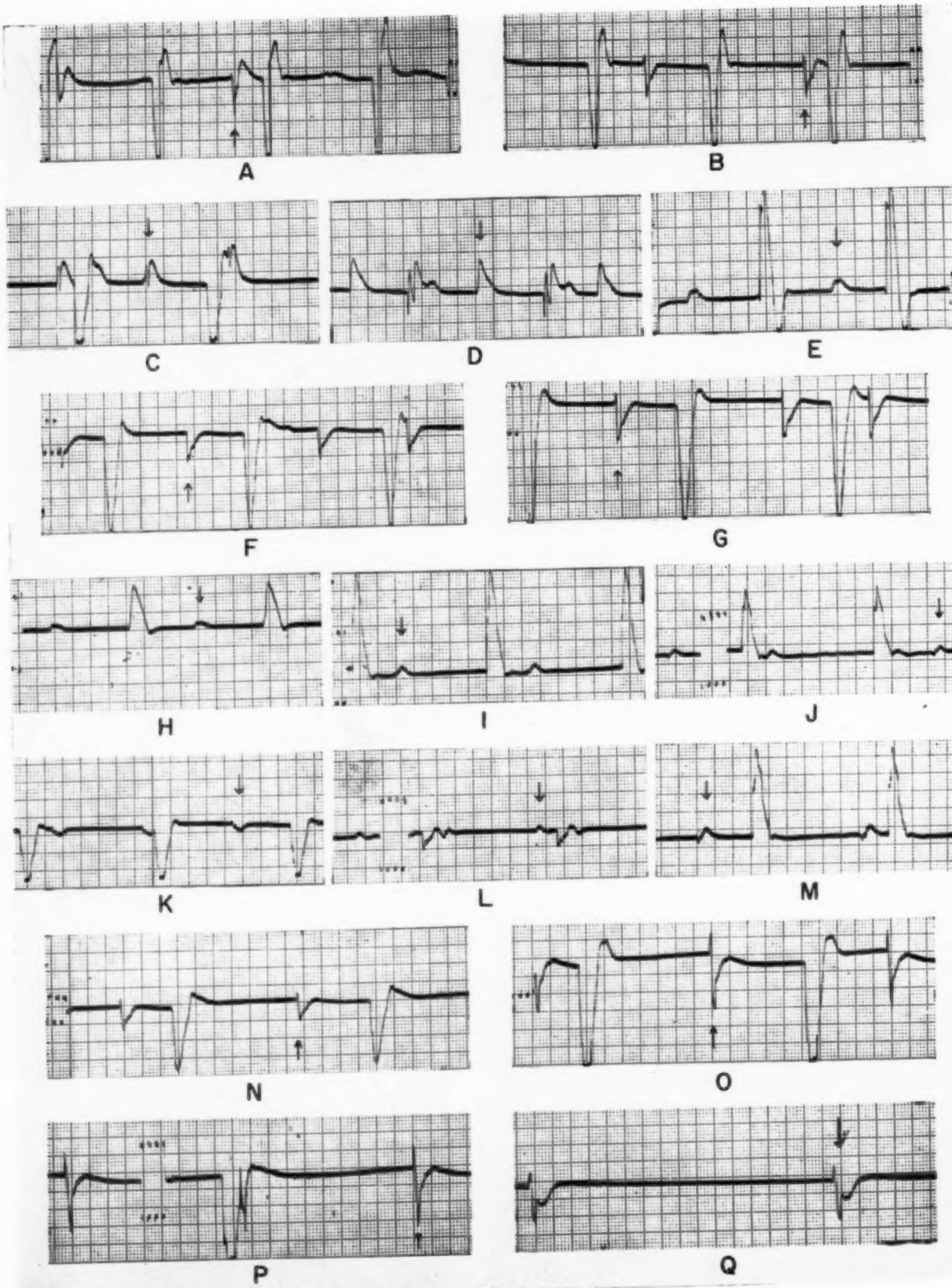

Fig. 4.—*(For legend see opposite page.)*

As the auricular anoxia continued, the contour of the P wave gradually assumed a wide bizarre configuration, although its predominant polarity was preserved; e.g., the bizarre right auricular lead P waves were still predominantly negative complexes (Fig. 4). The widening of these P waves was chiefly due to broadening of the auricular T wave. Auricular Q waves became apparent in standard Leads II and III and unipolar Lead aV_F (Fig. 4, I, J, M).

ARRHYTHMIAS AND OTHER CONDUCTION DISTURBANCES

Although auricular fibrillation and flutter were fairly common occurrences (Fig. 5), they were never long sustained. In contradistinction to the ventricles, which sometimes terminated activity in irreversible fibrillation, the auricles always ceased activity as a simple arrest (Fig. 4, Q). The method of producing injury, incurring total and equal anoxia, was probably significant in explaining this phenomenon.

Direct auricular leads have been published demonstrating auricular fibrillation and flutter,[3,14] but very few other conduction disturbances have been studied in this fashion. We observed the following conduction disturbances while recording direct auricular leads: auriculoventricular nodal rhythm, interference dissociation, fused complexes, wandering pacemaker, and various degrees of complete and incomplete auriculoventricular block (Fig. 6). Some of these were compared to their appearance in the same animals in the ordinary extremity leads.

When the ventricles of some dogs lapsed into fibrillation, this did not alter the basic auricular rhythmicity (Fig. 7). In the course of time, the ventricular fibrillation waves became smaller, making the auricular complexes more easily discernible. At this phase the direct auricular electrocardiogram resembles auricular fibrillation with complete auriculoventricular dissociation and idioventricular rhythm when seen in the indirect leads (Fig. 5,G).

Gross observation of the heart following injection of left intraventricular air demonstrated that ventricular activity was impaired long before that of the auricles. In the auricles, the cessation of grossly visible activity was in the following sequence: left auricular appendage, left auricle, right auricle, right auricular appendage. When the only myocardium visibly beating was that of the right auricular appendage, large distinct P waves were still recorded in the ordinary extremity leads (Fig. 4, H to M). Direct auricular leads at this time demonstrated entirely positive auricular complexes at both the left auricle and interauricular septum positions, indicating that electrical activation did not extend beyond the septum (Figs. 4, D; 7, I).

Fig. 4.—Demonstration of serial changes in the auricular and ventricular complexes as the length of total cardiac anoxia increases, leading to cardiac standstill. Representative segments of a continuous tracing from dog No. 5. Arrow in each segment denotes one of the P waves. Standardizations are included to show changes in galvanometer sensitivity. *A* and *B* are right auricular leads taken 8 minutes and 11 minutes, respectively, after air injection. Note that the auricular T wave becomes broader and lower. *C*, *D*, and *E* are at approximately the same time as *B*. *C* is a lead from the sulcus terminalis, *D* from the interauricular septal groove, and *E* from the left auricle. Note that the P wave in *D* and *E* is a monophasic positive complex. *F* and *G* are right auricular leads at 16 minutes and 21 minutes, respectively, after air injection. *H* to *M* are taken at approximately the same time as *G*. *H*, *I*, and *J* are standard Leads I, II, and III: *K*, *L*, and *M* are unipolar Leads aV_R, aV_L, and aV_F. Note the presence of an auricular Q wave in *I*, *J*, and *M*. *N* to *Q* are right auricular leads at 27, 32, 35, and 65 minutes after air injection. The arrow in *Q* points to the last evidence of electrical activity from the heart of this dog; there are no QRS's in this segment.

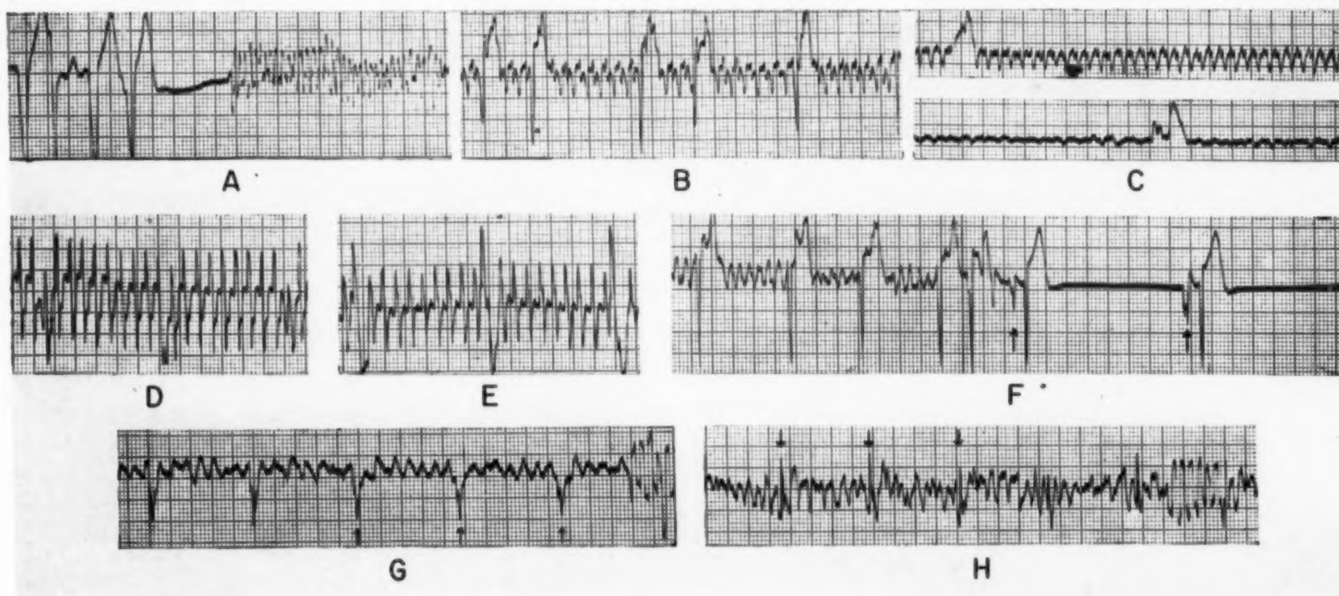

Fig. 5.—Auricular arrhythmias. *A* and *B* are right auricular leads from dog No. 4, 1 and 9 minutes after air injection. *A* marks onset of auricular fibrillation. *B* shows auricular flutter with varying ventricular response. *C*. Upper curve is 10 minutes after air injection, dog No. 4; note auricular flutter with single QRS; lower curve is aV_F at approximately the same time; note that the latter tracing resembles fibrillation rather than flutter. *D* and *E* are right and left auricular leads from dog No. 1, at a higher sensitivity than *B* or *C*, demonstrating auricular flutter with 10:1 block. *F*. Spontaneous abrupt termination of auricular fibrillation and resumption of sinus rhythm (arrows to P waves) in dog No. 4, right auricular lead. *G*. Ventricular fibrillation with regular P waves (arrows), 29 minutes after air injection, right auricular lead from dog No. 3. *H*. Auricular fibrillation with regular QRS's (arrows), 6 minutes after air injection, right auricular lead from dog No. 1. Note similarity of *G* and *H*.

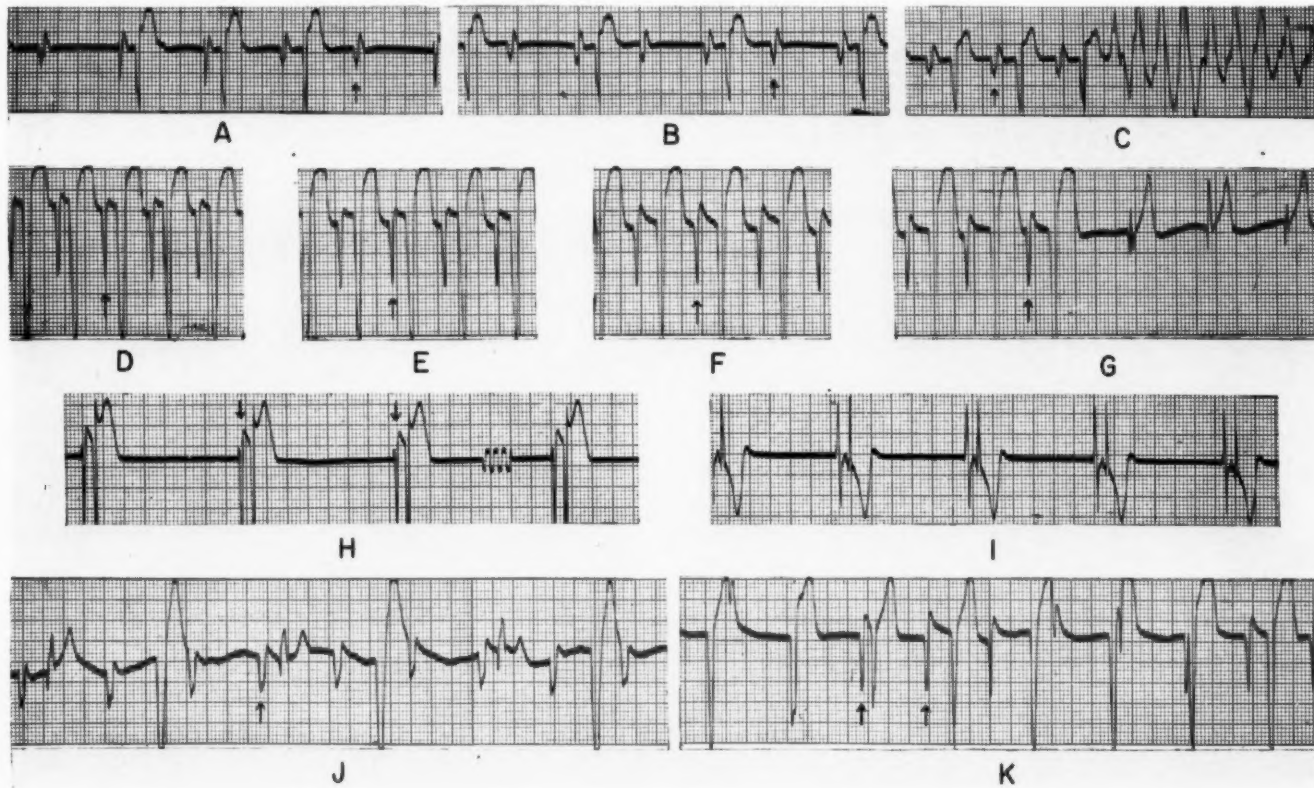

Fig. 6.—Conduction disturbances. *A.* Wandering pacemaker (or (?) intermittent impairment of auricular conduction with the same pacemaker), with blocked auricular beats, right auricular lead, dog No. 3. *B.* 2:1 atrioventricular block, right auricular lead, dog No. 3. *C.* Incomplete atrioventricular block with sudden onset of ventricular fibrillation, right auricular lead, dog No. 3. *D* to *G*, representative segments of continuous tracing from dog No. 2, demonstrating increasing P-R interval, with complete auricular arrest and onset of nodal rhythm in *G*; taken at ¾, 1¼, 1⅔, and 2¼ minutes after air injection. *H* and *I*. Fused auricular and ventricular complexes, right and left auricular leads, dog No. 2. *J* and *K* are right auricular leads from dog No. 2, 5½ and 9 minutes after air injection. *J* is interference dissociation; note completely regular basic auricular and ventricular rates, with varying response of the ventricles. *K* is complete atrioventricular dissociation without interference.

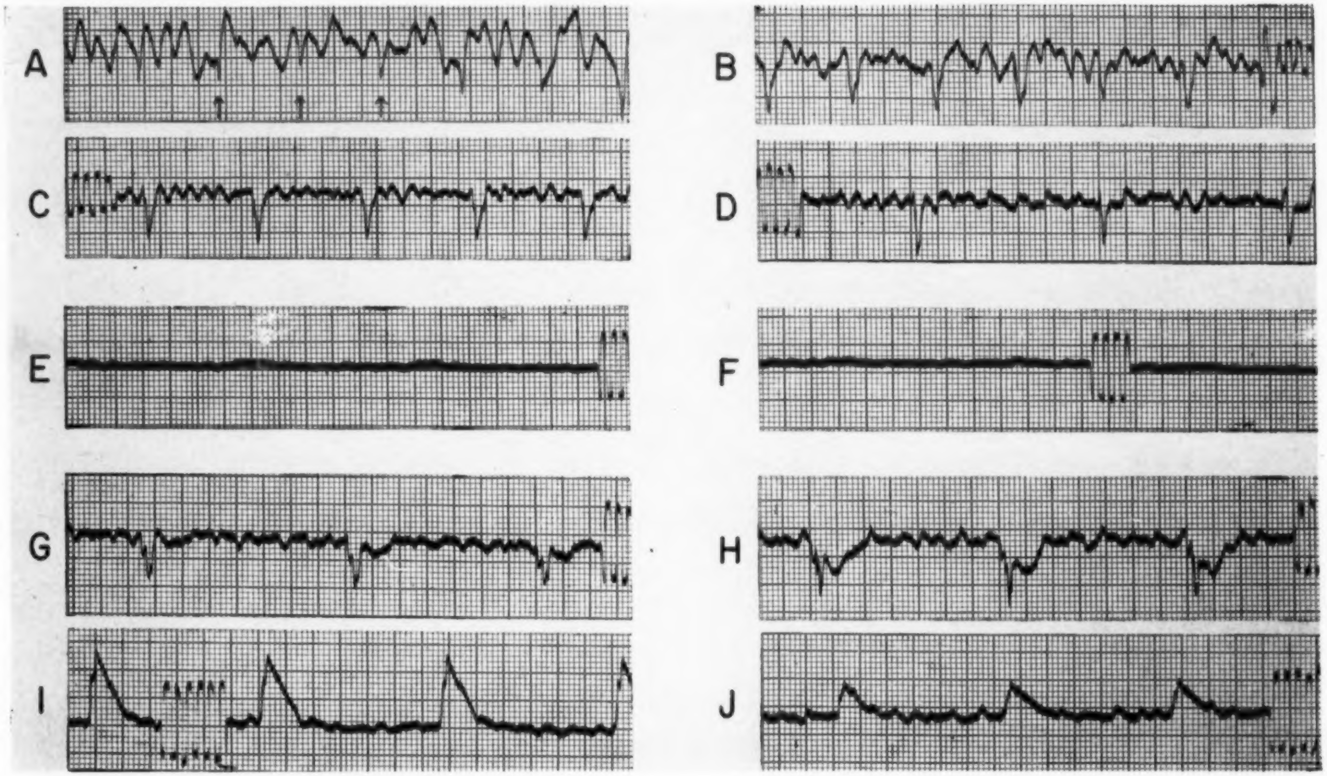

Fig. 7.—Auricular mechanisms during ventricular fibrillation. Representative segments of a continuous tracing from dog No. 3. *A* to *D*. Right auricular leads; 8, 13, 20, and 53 minutes after air injection. Arrows in *A* indicate the regularly occurring P waves, which become more apparent as the amplitude of the ventricular fibrillation waves subsides in *B* to *D*; note that the auricular rate is slowing. *E* and *F* are Leads II and aV_F, taken at approximately the same time as *D*; note absence of any discernible complexes. *G*, *H*, *I*, and *J* are at approximately 64 minutes after air injection and are from the position between the venae cavae, the sulcus terminalis, the interauricular septal groove, and the left auricle, respectively. Note the monophasic positive P wave from the septal groove and left auricle.

DISCUSSION

Infarction of the human auricles is probably more common than is generally supposed. Cushing and co-workers,[5] studying 182 autopsied cases of myocardial infarction, found auricular involvement in thirty-one (17 per cent). Although this is a higher incidence than that reported by most investigators, they felt that it was probably near the true incidence of such lesions, since the special studies required to detect such lesions are not routine during autopsies. Mural thrombosis (present in twenty-six of the thirty-one cases) and auricular rupture are two sequelae of auricular infarction which are of clinical significance.

From our foregoing data we must conclude that experimentally produced total cardiac anoxia has two separate effects on the heart. The first of these is myocardial ischemia, manifested in the electrocardiogram by $P\text{-}T_a$ or S-T segment displacement. The second is due to anoxia of the cardiac conduction system and is initially manifest by increasing auriculoventricular block, followed by arrhythmias and other conduction disturbances. The sudden onset of cardiac anoxia induced by air injection always produced $P\text{-}T_a$ and S-T segment displacement as an initial event, with aberrant conduction occurring later. By contrast we have previously observed that the gradual onset of cardiac anoxia following occlusion of the venae cavae evoked either of these two as an initial manifestation of injury with approximately equal incidence.[21]

This is the first demonstration of the simultaneous onset of auricular and ventricular injury patterns. Previous observations have suggested that electrocardiographic changes sometimes did not occur following experimental auricular injury. Our findings prove that with equal auricular and ventricular anoxia, the auricular changes in the electrocardiograms appear just as soon as the ventricular ones. In fact, the rapidity with which auricular injury patterns were observed raises the question of whether the auricular myocardium obtains any appreciable portion of its oxygen supply from the intra-auricular blood.

The monophasic positive P wave in some of our interauricular septal leads is a provocative finding. Although the spread of the auricular excitation wave is generally supposed to be equal in all directions, this monophasic P suggests that the excitation process does not pass the septal electrode. If this is true, impaired conduction along specific pathways is a more attractive explanation than some curtainlike syncytial block at the septum. Kishine and Musho,[22] in the solution of an intricate clinical electrocardiogram, also favored the existence of specific auricular pathways.

All published data on electrocardiographic changes following auricular injury, with the exception of some from esophageal leads, were obtained with the standard bipolar extremity leads. Although much attention has been given to the polarity of the auricular complex in the indirect leads, this became of relatively little significance when Wilson and associates demonstrated that such polarity was largely a function of cardiac position.[23] Our use of direct leads provides accurate localization regardless of the electric or anatomic axis of the heart.

In comparing the amplitude of P-T_a displacement to the amplitude of the P wave in direct auricular leads, we have been impressed by the fact that such displacement is usually less than half the amplitude of the preceding P wave. Thus, although P-T_a displacement is readily discernible in direct auricular leads, equivalent displacement in the indirect leads, where the P wave is much smaller in amplitude, could easily pass unrecognized. This helps explain the difficulty in making a correct diagnosis of auricular injury clinically.

We realize our experimental conditions differ in some respects from those encountered in clinical practice. With our method, however, there is little doubt that the entire oxygen supply of the auricles has been interrupted, a condition which has heretofore been difficult if not impossible to produce. We feel that this anoxic auricular injury more closely simulates that which occurs in human beings than any previously employed in the laboratory.

SUMMARY AND CONCLUSIONS

1. Experimental auricular injury has been produced by a new method, the injection of air into the left ventricular cavity. The advantages of this method are discussed.

2. Continuous direct auricular electrocardiograms were made until the cessation of all cardiac electrical activity. The sequential development of auricular changes was thus studied.

3. Auricular injury patterns with this method exhibited a consistent sequence in all animals. These began with a displaced P-T_a segment which evolved into a sharp auricular T wave. Initial evidence of injury appeared simultaneously in both the auricular and ventricular complexes.

We are grateful to Dr. Conrad R. Lam and Dr. F. Janney Smith for their suggestions in the preparation of this report.

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AURICULOVENTRICULAR NODAL RHYTHM WITH HEART BLOCK

RUSTOM JAL VAKIL, M.D. (LOND.), M.R.C.P. (LOND.)

BOMBAY, INDIA

AURICULOVENTRICULAR rhythm or auriculoventricular nodal rhythm or nodal rhythm is an infrequent cardiac disturbance where the pacemaking mechanism resides abnormally within the auriculoventricular nodal tissues. The electrocardiographic diagnosis of auriculoventricular nodal rhythm rests on (1) the character of the P wave, which being retrograde is usually inverted and spiky in Leads II and III, although upright but tiny in Lead I, and (2) the abbreviated duration of the P-R interval, which is never above 0.12 second.

Although the impulse from the auriculoventricular node usually spreads at normal speed, toward the auricles and ventricles, there are cases on record where the nodal impulse is delayed or even completely blocked, either on its way to the auricles (retrograde block) or on its way to the ventricles (antegrade block) (Drury,[1] Scherf,[2] Langendorf and associates[3].) In view of the extreme rarity of auriculoventricular block or antegrade block in cases of auriculoventricular nodal rhythm, the following two cases are recorded.

CASE REPORTS

CASE 1.—A Parsee gentleman, aged 70 years, has been under treatment for several years for essential benign hypertension, generalized arteriosclerosis and vitamin B_1 deficiency. From time to time, he has received and benefited from digitalis, diuretics, and thiamin hydrochloride injections, in the event of cardiac decompensation.

Prior to the onset of the first attack of nodal rhythm, his condition was as follows: the patient was symptomless, except for slight dyspnea on exertion and a long-standing dry cough. The peripheral arteries were palpably thickened, the blood pressure usually fluctuated between 150 and 170 mm. Hg systolic, and 88 to 108 diastolic. The apex beat, heaving and forcible, was felt in the fifth left intercostal space, three-fourth inch outside the mid-clavicular line. A systolic blowing bruit was audible all over the precordium, maximal in the aortic and mitral areas; the second sound was loud and metallic over the aortic area. A few moist sounds were usually audible over the lung bases.

An electrocardiogram recorded on Feb. 23, 1950 (Fig. 1, record *A*) showed a regular sinus rhythm with a rate of 74 per minute, upright P waves of normal contour, P-R intervals of 0.19 second, upright QRS complexes of normal duration and moderate voltage, slightly depressed S-T segments in Leads II and III, low and upright T waves in Leads II and III, and inverted or diphasic T waves in Lead III.

On the night of the same day, the patient experienced increasing dyspnea at rest and when examined a few hours later, exhibited a full-blown attack of acute pulmonary edema, with bubbling râles all over the lungs, bruit de galop over the heart, a loud second sound in the pulmonary area and copious and frothy expectoration. The blood pressure was 190/110 mm. Hg and the

From the Cardiological Department, King Edward Memorial Hospital, Bombay, India.
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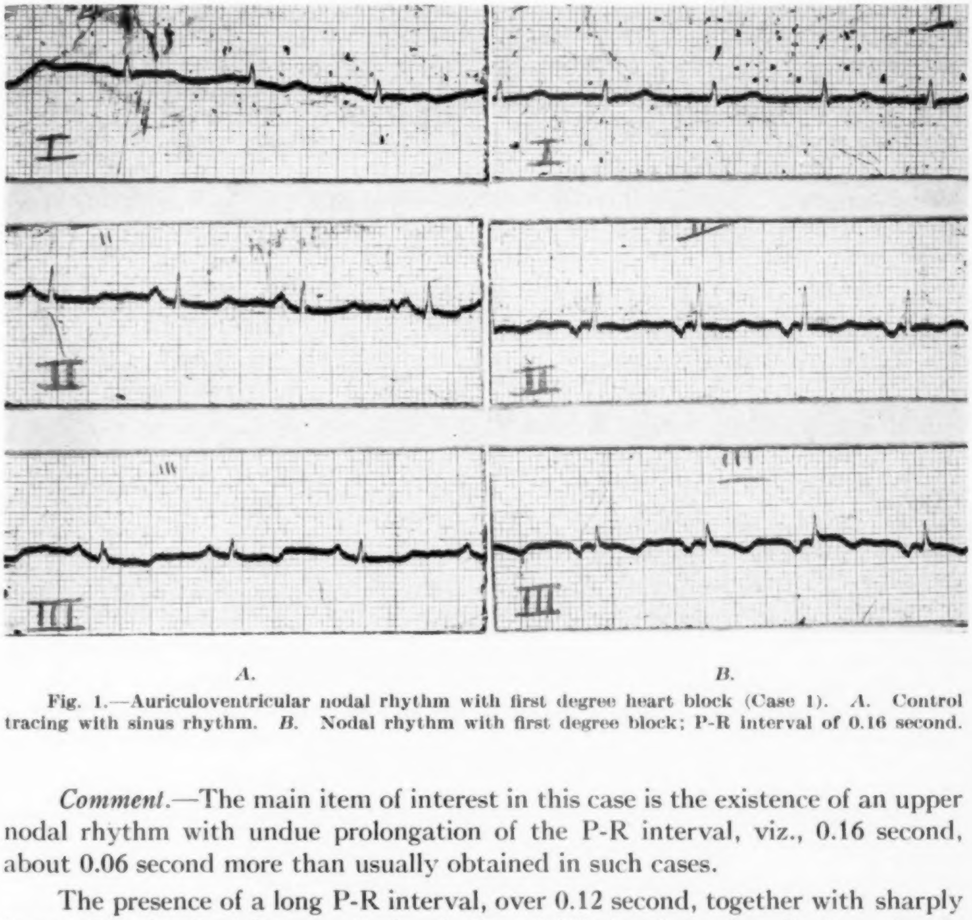
pulse about 132. After the injection of morphia, ¼ grain; atropine, 1/50 grain; and Pethidine, 100 mg., the patient felt better and went to sleep. The next morning, there were few symptoms or signs left of the attack, except for a general feeling of weakness or lassitude, a blood pressure of about 130 mm. Hg systolic and 80 diastolic and the low temperature of 97.4° F. The erythrocite sedimentation rate and white blood count were found to be within normal limits on Feb. 26, 1950. The electrocardiogram, taken on Feb. 24, 1950 (Fig. 1, *B*), shows a regular rate of about 82 per minute but with an upper auriculoventricular nodal rhythm. The diagnosis of auriculoventricular nodal rhythm is based on the presence of the deeply inverted and sharply peaked P waves or retrograde P waves in Leads II and III. The unusual feature about the tracing, however, is the duration of the P-R interval, viz., 0.16 second, which is 0.06 second longer than expected with upper nodal rhythm. The QRS-T complexes remain unaltered except for an increase in the degree of displacement of S-T segments and a reduction in the voltage of T in Lead II.

Repeated electrocardiographic tracings showed a persistence of the phenomenon, viz., upper nodal rhythm with a prolonged P-R interval with no other alterations for about six days.

On the seventh morning, after the onset of the attack of pulmonary edema, the electrocardiographic pattern had reverted to normal sinus rhythm with no residual abnormalities.

Since that time, the patient has been observed constantly for over two years, but the cardiac rhythm has never shown a tendency either to nodal rhythm or to auriculoventricular block.



A. *B.*

Fig. 1.—Auriculoventricular nodal rhythm with first degree heart block (Case 1). *A.* Control tracing with sinus rhythm. *B.* Nodal rhythm with first degree block; P-R interval of 0.16 second.

Comment.—The main item of interest in this case is the existence of an upper nodal rhythm with undue prolongation of the P-R interval, viz., 0.16 second, about 0.06 second more than usually obtained in such cases.

The presence of a long P-R interval, over 0.12 second, together with sharply inverted and spiked P-waves in Leads II and III, has been described previously

in the literature and attributed to one of three mechanisms: (1) a sinus rhythm with intra-auricular block, (2) a special variety of coronary sinus nodal rhythm (Zahn[4]), and (3) an auriculoventricular nodal rhythm associated with delayed antegrade conduction or with first degree auriculoventricular heart block (Langendorf and associates[3]). After a critical analysis of these theories, Langendorf and his associates[3] came to the conclusion that every instance of such a rhythm represents auriculoventricular nodal rhythm with auriculoventricular block, rather than the two alternative explanations.

In view of (1) the transient nature of the cardiac arrhythmia in our case, lasting only 6 days, (2) the sudden onset of the arrhythmia, coinciding with the attack of acute left ventricular failure with pulmonary edema, and (3) the simultaneous occurrence and disappearance of the two pathologic phenomena of nodal rhythm and first degree heart block, one is inclined to attribute the phenomenon to a fairly extensive but reversible cardiac injury, involving both the pacemaker of the heart as well as the auriculoventricular functional tissue immediately below the site of nodal impulse function. This might have been induced by the acute left ventricular failure. The question of a localized myocardial infarct (auricular) was entertained but considered unlikely in view of (a) the absence of the customary pyrexia, leucocytosis and increased sedimentation rate, and (b) the sudden appearance of, the lack of cyclical variation in, and the sudden disappearance of the electrocardiographic pattern.

CASE 2.—The patient, an Englishman, aged 30 years, was first examined for attacks of giddiness or vertigo, accompanied at times by palpitation or faintness. At no time had he experienced any dyspnea, precordial or substernal pain, or given a history suggestive of a coronary accident.

Apart from a history of several attacks of sore throat and vague aches and pains, on and off, in the joints, there was no definite history of rheumatic fever or any other ailment. The family history was also negative.

According to the patient, for several months before admission, there had been sudden attacks of giddiness or faintness with or without palpitation, lasting for seconds, minutes, or hours and not related in any way to exertion, emotion, or meals. During such attacks, he had never had any dyspnea, pain, or sweating.

On examination, he was a healthy-looking individual with no evidence of dyspnea, pallor, or cyanosis, venous engorgement or edema. The chest was symmetrical, the apex beat was normal, and both were seen and felt in the fifth left intercostal space, one-half inch inside the midclavicular line. On palpation, no thrills were felt but a diastolic shock was experienced in the pulmonary area. On auscultation, there was a Grade 2 systolic bruit, maximal at the mitral area and conducted to the axilla, as well as an accentuation of the second sound in the pulmonary area. The pulse was found to vary within a matter of minutes (even at the first examination), from being normal in rate and regular to slow and irregular. The blood pressure was 126/78 mm. Hg, the body temperature and respiration rate, normal. Fluoroscopy revealed only a mild degree of left ventricular hypertrophy with no evidence of any other abnormality.

On the grounds of the above findings and history, a tentative diagnosis of rheumatic mitral incompetence was entertained and the patient subjected to a critical electrocardiographic investigation. Over a period of about six months, well over 25 electrocardiographic records were obtained and analyzed. It was soon obvious that these records could be sorted into four groups, as follows: (1) some with regular sinus rhythm; (2) some with regular upper nodal rhythm; (3) some with upper nodal rhythm and regular ventricular bradycardia; and (4) some with arrhythmic upper nodal rhythm and ventricular arrhythmia.

A description follows of the four types of electrocardiographic patterns obtained from time to time in the present case. The electrocardiographic picture on this patient appeared to be in a state of constant fluctuation, reversion from one type of tracing to another being noted within a matter of minutes or seconds and for no apparent reason (see Fig. 2).

Description of electrocardiographic tracings in Fig. 2: Record *A* shows a sinus rhythm with a mild degree of sinus arrhythmia, the rate varying between 78 and 84 per minute. The P waves are upright and normal in contour, the P-R interval in Leads II and III is 0.13 second, the electrical axis is normal, the QRS complexes are normal in contour and duration (0.08 second), the S-T segments and T waves are normal.

Record B_1 shows a regular rhythm and a rate of 90 per minute. The P waves are tiny and upright in Lead I, but large, spiky and deeply inverted in Leads II and III. The P-R interval is 0.09 second (being 0.04 second less than in record *A*). In view of the contour and direction of the P waves and the duration of P-R, a diagnosis of upper nodal rhythm is made. The QRS complexes are normal, but there is definite aberration of the S-T-T segment, suggestive of a "coronary" pattern, viz., upwardly displaced and convex S-T segments with inverted T waves in Leads II and III.

Record B_2 was taken soon after B_1 to show the effect of an intravenous injection of 1/50 grain atropine sulphate on the cardiac arrhythmia. As will be obvious from a comparison of the two records, the electrocardiographic pattern remains unaltered after atropinization.

Record *C* displays a complex arrhythmia. The large and inverted P waves of nodal rhythm are easily discerned in Leads II and III; the rate of the auricle varies from 107 to 114 per minute in the record, there being a nodal tachycardia with some degree of nodal arrhythmia. The retrograde P waves are likely to be confused at first sight, with the somewhat similar inverted T waves but are slightly different in amplitude and contour. The ventricular rate is exactly one-half that of the auricular, being 54 to 57 per minute. The P-R interval, in Leads II and III, is 0.10 second. In view of the 2 to 1 relationship between the retrograde auricular waves and the ventricular complexes, a diagnosis of upper nodal rhythm with 2 to 1 auriculoventricular block or antegrade block is made. The S-T-T complexes, in this record, are definitely suggestive of a coronary pattern.

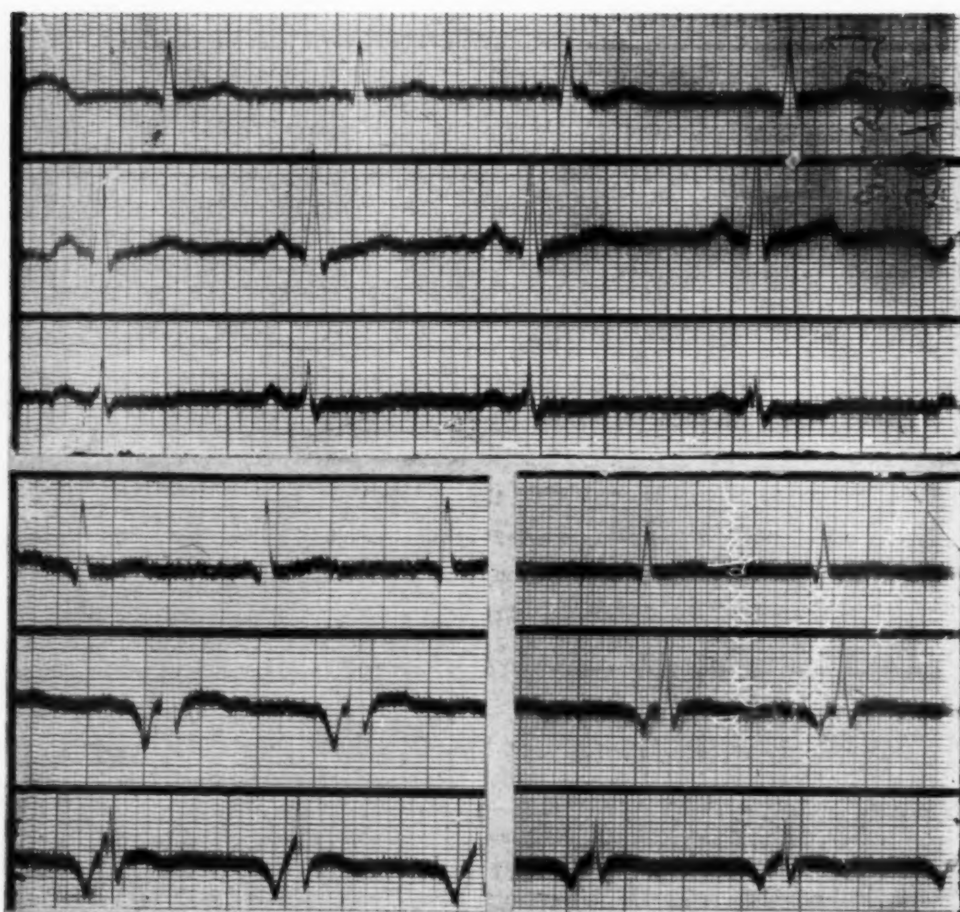
Record *D* is similar to record *C* except for the addition of other abnormalities. There is a regular auriculoventricular nodal rhythm or a "nodal tachycardia" with a rate of 108 per minute; the ventricular complexes have an inherent rate of 54 per minute or exactly one-half that of the auricles. Closer scrutiny reveals a gross degree of ventricular arrhythmia in Leads II and III. The nature of this arrhythmia becomes obvious on following up systematically the inverted P waves in Leads II and III. In Lead II, the first retrograde P wave is not followed by a QRS complex, there being a complete antegrade block to the nodal impulse; the second P wave is followed by a QRS complex after an interval of 0.10 second as in record *C*. The QRS is followed by a sharply inverted T wave, somewhat akin in shape to the retrograde P; the third P wave (P_3) is grossly delayed in its appearance considering that the spacing of the P-P intervals has been 0.56 second throughout record *C* and in most of record *D*; the P_2-P_3 interval is 0.9 second, or almost double the usual interval. The cause of this delay in the appearance of P_3 will be discussed later. P_3 is followed by a QRS with its inverted T wave. Next comes a retrograde P wave (P_4), the P_3-P_4 spacing being 0.56 second as usual. In accordance with the 2 to 1 auriculoventricular block routine, observed in record *C* and in part of *D*, it is rather surprising to see a QRS-T complex follow P_4. Although the complete antegrade block is not observed as expected, there is, however, a marked delay in conduction time, a first degree heart block or partial heart block; the P-R interval is 0.20 second or exactly double the customary figure. Next in Lead II appears another retrograde P wave to be followed at the customary interval of 0.10 second, by a QRS-T complex.

A similar follow-up of Lead III in record *D* reveals two retrograde P waves (P_1 and P_2), the second being followed by a QRS complex and inverted T wave. The next P (P_3) follows after an unusually long P_2-P_3 interval of 0 to .88 second, another instance presumably of a nodal pause or nodal standstill. P_3 is followed by a QRS complex and T wave, after which continues the same pattern of events as observed in record *C*.

Comment.—The most striking feature about this case is the instability of the electrocardiographic picture, there being a constant reversion from one type of electrocardiographic picture to another. After a study of all the electrocardiographic tracings taken over a period of several months, four distinct types of electrocardiographic tracings could be sorted out, as exemplified in records *A*, *B*, *C*, and *D*, respectively.

Several of the electrocardiographic abnormalities observed in records *B*, *C*, and *D* require further amplification. The dominant rhythm in all three records is a nodal or auriculoventricular nodal rhythm of the upper nodal type. The rate of the nodal rhythm, in the present case, is unusual, being 90 per minute in record *B*, 107 to 114 per minute in record *C*, and 108 per minute in record *D*. The average nodal rate is said to be from 35 to 50 per minute (Katz[5]). The rates

A.



B_1 B_2

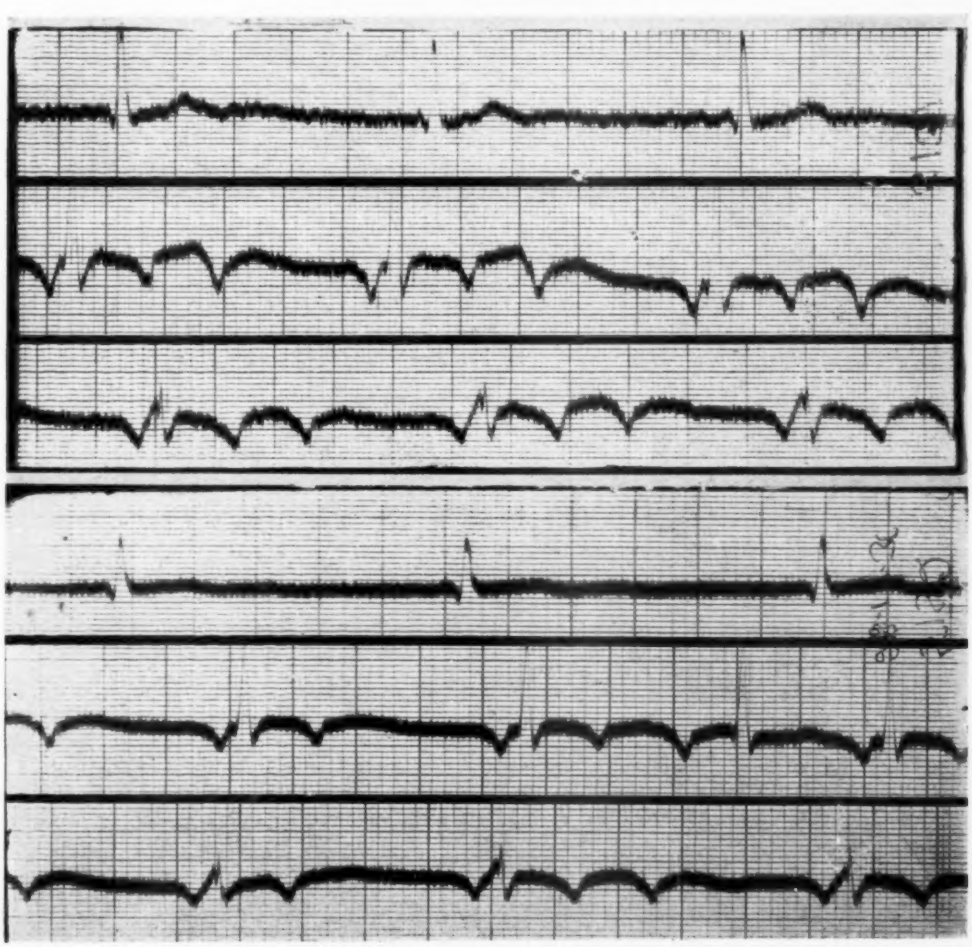
Fig. 2.—Auriculoventricular nodal rhythm with heart block (Case 2). *A*. Control tracing with sinus rhythm. B_1. Upper nodal rhythm; rate 90 per minute; aberration of S-T-T segment. B_2. Same after intravenous injection of 1/50 grain atropine sulphate.

observed in the present case are therefore unusual. It is logical to label the nodal rhythm in records *C* and *D*, with an inherent discharge rate of over 100 per minute, as "nodal tachycardia" rather than as nodal rhythm proper.

Another feature of interest about the nodal rhythm in this case was the arrhythmia accompanying it in record *C*, the rate fluctuating between 107 and 114 per minute. Such a mild degree of arrhythmia does occur at times as an accompaniment of nodal rhythm. In records *B* and *D*, on the other hand, the nodal rates were constant, being 90 and 108 per minute, respectively.

The lack of response of the nodal rhythm to intravenous Atropine (see records B_1 and B_2) tends to exclude a vagal origin for the arrhythmia. Such is more in favor of a refractory pathologic lesion in the myocardium.

C.



D.

Fig. 2.—(*Continued.*) *C.* Nodal rhythm with nodal tachycardia, 2 to 1 antegrade block and coronary type of S-T-T segment. *D.* Nodal rhythm with nodal tachycardia, varying degree of antegrade block, nodal pause, and coronary type of S-T-T segment.

In records *C* and *D*, the auricular rate (i.e. of the retrograde P waves) is exactly double that of the ventricles, the auricular rate being 107 to 114 per minute in record *C* and 108 per minute in record *D*, the ventricular rate being 54 to 57 per minute in record *C*, and 54 per minute in record *D*. In other words, although all impulses generated at the auriculoventricular node are conducted efficiently to the auricles (retrograde conduction normal), every alternate impulse gets blocked completely, on its way to the ventricles, an example of a 2 to 1 antegrade, or auriculoventricular block in association with nodal rhythm. Cases of both antegrade and retrograde block in association with nodal rhythm are on record (Drury,[1] Scherf,[2] Langendorf and associates[3]). It is possible to suggest as an explanation, for the 2 to 1 antegrade block in records *C* and *D*, the rapid discharge rate of the auriculoventricular node. It is possible that with a nodal rate of 90 per minute as in records B_1 and B_2 every nodal impulse can be transmitted to the ventricles but with faster rates of over 100 per minute, as in records *C* and *D*, where the auriculoventricular conducting pathway proves incapable of transmitting all nodal impulses and a 2 to 1 antegrade block develops.

The ventricular rate, although constant in records *A*, *B*, and *C*, reveals an interesting form of arrhythmia in Leads II and III of record *D*. This is due, mainly, to the unusually long P_2-P_3 intervals, in Leads II and III. Instead of the customary P-P interval of 0.56 second, the P_2-P_3 in Lead II is 0.90 second, and in Lead III, 0.88 second. Some sort of explanation is needed for this anomalous behavior in the otherwise regular rate of discharge of the auriculoventricular node. The following explanations suggest themselves, (a) this may be due to a nodal arrhythmia; such an explanation is unlikely, considering that the remaining P-P intervals are quite constant in duration (0.56 second); (b) it is possible that during these two long pauses in Leads II and III of record *D*, a nodal impulse might have been normally generated but has failed to register itself in view of a superadded retrograde block (in addition to the customary 2 to 1 antegrade block). Such an explanation is unlikely, in view of the fact that the P_2-P_3 interval is not an exact double or multiple of the customary P-P interval of 0.56 second; (c) the third and most likely explanation, in my opinion, for the wise spacing of P_2-P_3, is the possibility of a "nodal pause" or "nodal standstill," somewhat akin to the well-recognized phenomenon of sinus pause or sinus standstill.

The undue prolongation of the P-R interval (0.20 second, witnessed in Lead II, Record D) following the auricular wave P_4 requires some sort of explanation. Instead of the customary short P-R of upper nodal rhythm (viz., 0.10 second, as seen in the rest of the record, the P_4-R interval is exactly double or 0.20 second. This is probably an isolated example of a first degree or partial heart block with a gross delay in the conduction of the nodal impulse toward the ventricles. Instead of a complete antegrade block as witnessed elsewhere, there is here an isolated instance of a partial or incomplete block.

Another feature of interest in this case was the behavior of the ST-T complex. During phases of normal sinus rhythm (record *A*, Fig. 2), the S-T segments and T waves were normal in all respects. During phases of uncomplicated nodal rhythm (record *B*, Fig. 2), the S-T segments of Leads II and III invariably showed

upward displacement with a convexity upward and followed by inverted T waves. During phases of nodal rhythm complicated by auriculoventricular block (records *C* and *D*, Fig. 2), the abnormalities of the S-T segment and T wave, although of similar nature, were even more marked. The S-T-T complex abnormalities of Records *B*, *C*, and *D* are suggestive of a "coronary pattern," the so-called "elevated S-T type" of coronary electrocardiogram (Katz[5]). In the present case, however, the S-T-T abnormalities were strictly transitory, occurring only during phases of nodal rhythm, and in a more accentuated form during phases of auriculoventricular nodal rhythm with auriculoventricular block. Why this state of "myocardial anoxia" or "relative coronary insufficiency" should have arisen during every phase of nodal rhythm cannot be answered.

In view of the constant variation of the electrocardiographic picture in this case, the cardiac rhythm alternating between sinus rhythm, uncomplicated nodal rhythm and nodal rhythm with auriculoventricular block, sometimes within a matter of minutes or hours and for no apparent reason, one is inclined to suggest the operation of some vascular or neurogenic factor rather than a pathologic lesion in the genesis of the cardiac arrhythmia. This contention is further supported by the strange behavior of the S-T-T complex during phases of the arrhythmia.

SUMMARY

Two cases of upper nodal rhythm associated with auriculoventricular heart block or antegrade block are presented.

The first case shows the transitory development of an upper nodal rhythm with first degree auriculoventricular heart block, in an elderly hypertensive patient, soon after an attack of acute pulmonary edema.

The second case is of unusual interest, exhibiting as it does phases of (1) normal sinus rhythm, (2) uncomplicated upper nodal rhythm, (3) nodal tachycardia with 2 to 1 auriculoventricular antegrade block, and (4) nodal tachycardia with instances of 2 to 1 block, first degree heart block, and nodal pauses. Another feature of unusual interest is the regular appearance of a coronary S-T-T pattern during phases of nodal rhythm.

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PRESSURE PATTERNS FROM THE CORONARY VENOUS SYSTEM IN MAN

G. Miller, M.D., B. M. Kaplan, M.D., and L. N. Katz, M.D.

Chicago, Ill.

In the course of catheterization studies of the right side of the heart, a number of investigators[1-13] have either intentionally or inadvertently entered the coronary sinus. In view of the complications that may arise from such an occurrence,[2,3] it is important to be able to recognize the location of the catheter constantly. In addition to the undesirable sequelae which may ensue from the unrecognized prolonged placement of the catheter in the coronary sinus much of the time alloted for roentgenographic exposure will be wasted. It is obviously necessary to recognize the variety of pressure curves obtained from the coronary venous tree and to be able to differentiate them from pressure curves obtained from the heart chambers, which they resemble. Relatively little information is available on the factors which determine and modify the contour of the pressure curves of the coronary venous tree. The present report is an attempt to fill this gap. It concerns itself primarily with pressure curves obtained from ten patients in whom the catheter inadvertently entered the coronary sinus during right-sided heart catheterization. The practical aspects of promptly recognizing such an event are discussed.

METHODS

Right-sided heart catheterization was performed with all patients in a post-absorptive state. Pressures were taken with capacitance type electromanometers* recording on a direct-writing polyoscillograph.* The zero level for all pressures was taken as 5 cm. below the angle of Louis, and pressures were standardized with a mercury manometer. Gas analyses of blood samples were performed according to the method of Van Slyke and Neill.[14]

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill.

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*Sanborn Company, Cambridge, Mass.

RESULTS

The data are summarized in Tables I and II and typical records are shown in Figs. 1 to 4.

TABLE I. OXYGEN DATA OBTAINED

CASE	DIAGNOSIS	OXYGEN CONTENT			OXYGEN CAPACITY VOL. (%)	(%) OXYGEN SATURATION	
		CORONARY SINUS VOL. (%)	RIGHT VENTRICLE VOL. (%)	BRACHIAL ARTERY VOL. (%)		CORONARY SINUS	BRACHIAL ARTERY
1	Eisenmenger's complex	4.7	13.5	16.5	18.7	24	88
2	Interauricular septal defect with questionable pulmonary stenosis	2.8	*	12.4	14.1	20	88
3	Normal heart, pulmonary tbc.	5.3	*	21.3	21.7	24	98
4	Eisenmenger's complex	5.5	18.4	21.7	24.3	23	89
5	Single ventricle, truncus aorticus solitarius	5.8	16.3**	16.6	20.1	29	82
6	Interauricular septal defect	4.7	13.7	17.1	18.4	26	93
7	Undiagnosed congenital heart disease, auricular fibrillation	6.1	19.3**	18.3+	21.9	28	84
8	Interauricular septal defect	5.1	11.0†	20.4‡	22.8	22	95‡
9	Questionable pulmonic stenosis	5.2	14.3	17.1	19.5	27	89
10	Interventricular septal defect, possible tetralogy of Fallot	5.4	16.8	15.8	18.8	29	84

*Not stated or not obtained.
**Common ventricle.
+Taken at another time.
†From right auricle.
‡From a pulmonary vein.

In one patient (Case 1), five distinct types of coronary venous system pressure curves were obtained. At the mouth of the coronary sinus, low pressures were obtained (Fig. 1, *A*). As the catheter was inserted more deeply, higher pressures were noted as a rule although an occasional low pressure was recorded. The contour of the coronary venous curves in this patient at times resembled that of those taken from the right ventricle a few minutes later (compare Fig. 1, *B*, *C*, *D*, and *E* with Fig. 1, *F*). The sharp rise in coronary venous pressure did not begin at the onset of systole, but instead it generally began during systole; at one site, however, the rise actually began during diastole (Fig. 1, *B*). The systolic pressure maximum obtained from the coronary tree, in this patient, varied from 1 to 83 mm. Hg, while the diastolic pressure varied from −5 mm. Hg to + 12 mm. Hg.

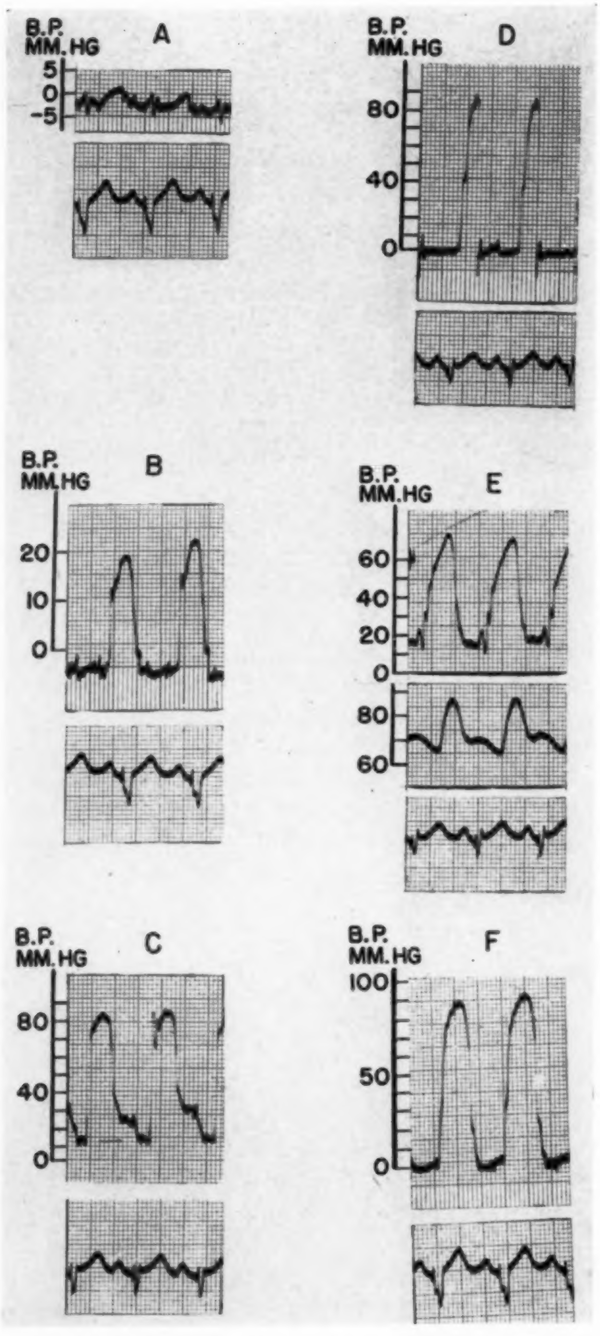

Fig. 1.—Pressure pulses in patient No. 1. In each segment except *E* the lower curve is Lead II of the electrocardiogram simultaneously recorded with the pressure pulse. In *E*, this is the lowest curve. Time is given in the abscissae as 0.04 and 0.2 sec. Ordinates give pressures as indicated in calibration at left. In *A*, *B*, *C*, and *D* the upper curve is from the coronary venous tree and so is the uppermost curve in *E*. The middle curve in *E* is from the femoral artery and the upper curve in *F* is from the right ventricle. The various contours of the pressure pulses from the coronary venous tree are shown by these segments. In *A* the curve resembles an auricular pressure pulse; in *B*, *C*, *D*, and *E* the resemblance to a ventricular pressure curve (with phase displacement and some artifacts) is obvious. Discussed in text.

The pressure curves in patients 2 and 3 (65/11 mm. Hg and 25/10 mm. Hg pressure, respectively) bore a resemblance to those ordinarily obtained from the right ventricle except for timing. In patient 4, a pressure obtained at the mouth of the coronary sinus was 8/3 mm. Hg and the curve resembled an auricular tracing (Fig. 2). The pressure curves from deep in the coronary venous system

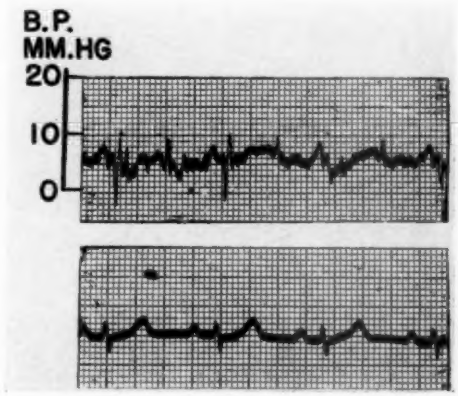

Fig. 2.—Pressure pulses in patient No. 4. Conventions as in Fig. 1. Pressure pulse was obtained from the mouth of the coronary sinus and resembles an auricular type of curve. Discussed in text.

TABLE II. PRESSURE DATA OBTAINED

CASE	CORONARY VENOUS SYSTEM MM. HG	RIGHT VENTRICLE MM. HG	RIGHT AURICLE MM. HG	LEFT VENTRICLE MM. HG
1	9/−4 20/−5 57/3 80/12 83/−1	95/0	3/−3	
2	65/11	*	12/7	90/6†
3	25/10	*	*	
4	8/3	99/6	6/0	
5	51/14	88/12**	13/9	
6	35/10 48/10 55/8 10/4	56/6	6/4	
7	60/8	110/10**	10/6	
8	11/0	78/3	12/4	
9	28/6	30/2	10/3	
10	8/0	95/8	6/2	

*Not obtained.
**Common ventricle.
†Left ventricle entered via interauricular septal defect and left auricle.

in patient 5 were similar to right ventricular pressure curves, although there was a sloping rise to a pointed peak in the coronary curves as contrasted to the right ventricular curves in this patient (compare Fig. 3, *A* with Fig. 3, *B*). Patient 6 presented both an auricular and ventricular type of curve, such as was noted in patient 1. Ventricular types of curves were also seen in patients 7 and 9, while an auricular type was recorded in patients 8 and 10; especially striking were the large "a" waves noted in patient 8 (Fig. 4).

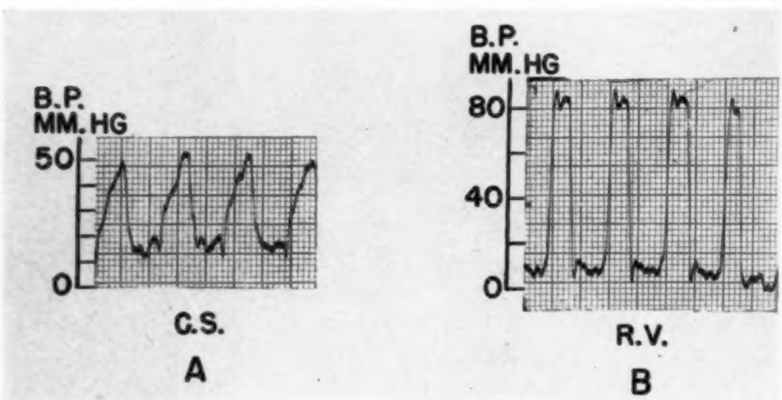

Fig. 3.—Pressure pulses in patient No. 5. Conventions as in Fig. 1, but the simultaneous electrocardiograph has been omitted. In *A* is shown a pressure pulse recorded from deep within the coronary venous system. In *B* is shown the right ventricular pressure pulse. Like Fig. 1, *E*, the coronary pressure pulse here has a distorted ventricular form. Discussed in text.

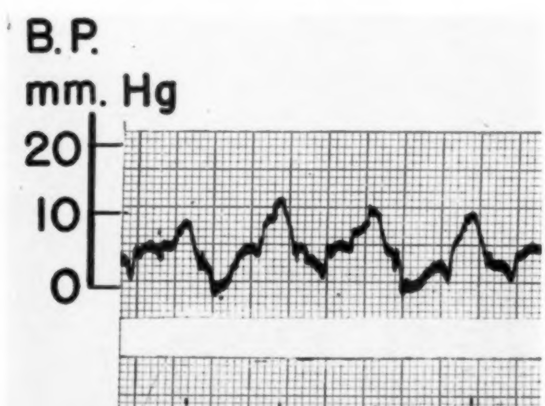

Fig. 4.—Pressure pulse in patient No. 8. Conventions as in Fig. 1. Pressure was obtained from the mouth of the coronary sinus and resembles an auricular type of curve with a large "a" wave. Discussed in text.

We observed no special arrhythmias in any of these patients while the catheter was in the coronary sinus (cf. Fig. 1). In patient 7, auricular fibrillation was present prior to catheterization, and this continued during the entire procedure. In several patients premature beats were noted while the catheter was in the coronary sinus, but this is a common occurrence during catheterization of the heart chambers and was not more frequent during catheterization of the coronary venous system. In patient 4, a transient widening of the QRS complex occurred while the catheter was in the right auricle, and this recurred while the catheter was deep in the coronary venous system. No patient had electrocardiographic evidence of myocardial ischemia as a result of the catheterization.

The oxygen saturation of the blood samples taken from the coronary venous system in the ten patients varied from 20 to 29 per cent. The oxygen contents varied from 2.8 to 6.4 vol. per cent (see Table I).

DISCUSSION

The recognition of the presence of the catheter in the coronary venous system is of practical importance since serious damage may result from deep catheterization of the coronary sinus.[2,3] Goodale and associates demonstrated mural thrombi and hemorrhages in the coronary sinus and right auricle, as well as coronary venous thrombosis and gross hemorrhages into the myocardium following catheterization of the coronary venous tree in dogs.[4,5] Smith and co-workers[2] reported a case with peripheral vascular collapse and electrocardiographic changes characteristic of pericarditis following coronary sinus catheterization. McMichael and Mounsey[3] presented five cases with adverse reactions to deep catheterization of the coronary venous tree. All five of their patients complained of precordial or back pain and three showed evidence of peripheral vascular collapse with electrocardiographic changes typical of pericarditis. We were fortunate in not encountering any of these complications.

Generally, one can check the location of the catheter tip by observing the pressure curves recorded at a particular site. However, the pressure curves obtained from the coronary sinus may simulate those of the right ventricle or right auricle both in contour and magnitude and thus lead to faulty conclusions.[7-9] In one patient, we observed several pressure curves from the coronary venous system which could be mistaken for right ventricular pressures (Fig. 1), except that there was phase displacement. Thus, the onset of the pressure curve did not begin with the beginning of systole but occurred during systole or even during diastole. This we consider is of diagnostic significance. Furthermore, the peaked summits, and the retarded and the notched upstroke, present in Fig. 1, *E* and Fig. 3, and the notched slow descent from the systolic peak (Fig. 1, *C*) are not ordinarily seen in right ventricular curves. Pressure curves resembling those obtained from the right auricle were also obtained when the catheter was near the orifice (Figs. 1, *A*, 2, and 4).

It is likely that the variety of curves recorded from the coronary venous system is due to a number of factors, the most important of which is the position of the catheter. If the catheter completely plugs the vein, the contraction of

the myocardium about the occluded vessel will elevate the intraluminal pressure at the catheter tip and record a systolic pressure and pulse curve that approximate the intraventricular, except for phase displacement and notchings. In diastole, as the vein becomes patent the pressure within it drops sharply as does the pressure in the ventricular cavity. Thus, it might be anticipated that the pressures obtained from deep in the coronary venous system could mimic those obtained from the right ventricle and at times even those of the left ventricle.* (Gregg[15] has shown that acute coronary sinus closure in dogs causes a greatly elevated pressure in the coronary sinus and great cardiac veins, often approximating or exceeding aortic systolic pressure.) The cause of the diastolic pressure rise noted in patient 1 (Fig. 1, *B*) is uncertain. This rise could represent drainage from the coronary artery into a superficial coronary vein obstructed during diastole only.

The pressure curves obtained at the mouth of the coronary sinus are auricular in type, (see Figs. 1, *A*, 2, and 4) and can be ascribed to direct transmission of pressure from the right auricle to the catheter tip. The giant "a" wave seen in patient 8 (Fig. 4) has been found by Gregg[15] in dogs when recording from the coronary sinus or the ostium of an anterior coronary vein.

Variations in contour of the pressure pulse from the coronary venous system obtained in different patients and even in the same patient may be due to several factors: (1) the degree of occlusion of the coronrary vein by the catheter, (2) phase of the cardiac cycle in which occlusion is present, (3) the location of the catheter in relation to the contracting myocardium (i.e., superficial or deep within the myocardium, or inserted far into the coronary venous tree or at the mouth of the coronary sinus), (4) respiratory variations.

The contour of the pressure curves obtained in the coronary venous system may serve to fix the exact location of the catheter tip. When pressure curves of different contour are obtained with minor shifts in the catheter, the suspicion should be entertained of having inserted the catheter far into the coronary venous system. However, certainty as to whether or not the catheter is in the coronary sinus is verified by determination of oxygen saturation of a blood sample. Our findings (Table I) are in accord with the literature in showing oxygen saturation of coronary sinus blood between 20 and 30 vol. per cent. The oxygen content of the blood from the coronary venous tree varied from 2.8 to 6.4 vol. per cent,† in agreement with previous findings.[1,7,10,11] The dark color of the coronary sinus blood often permits the person drawing the sample to suspect it immediately. This sort of quick inspection can easily be accomplished when necessary.

In fluoroscoping in the posteroanterior view, it is impossible occasionally to tell whether the catheter is in the right ventricle, main pulmonary artery, or deep in the coronary sinus. Rotation of the patient to the left anterior oblique

*Such deformations of ventricular pressure curves in the cavity of the ventricles are due to artifacts; these can ordinarily be avoided by slight shift in the location of the catheter. This is not true in the coronary venous system.

†In this report, we have not included a number of other instances of inadvertent entry of the catheter into the coronary sinus as judged by pressure curves, because no blood sample was obtained to verify this opinion.

position has been recommended to eliminate such doubt concerning the location of the catheter.[3] Likewise, the right oblique position has been used to help detect entry into the coronary sinus, while passing the catheter through the tricuspid valve.[2] Such shifts in position can be undertaken when necessary.

As a result of a critical analysis of the pressure pulse curves obtained in these ten patients, we feel that we are able to recognize entry of the catheter into the coronary sinus during the course of right-sided heart catheterization. As a consequence immediate withdrawal of the catheter from the coronary sinus has become routine during the past year whenever the pressure curves were suspicious.*

SUMMARY

1. During the right-sided heart catheterization of about 250 patients proof of inadvertent entry into the coronary venous system was observed and confirmed in ten patients.

2. The pressure pulse patterns from the coronary venous tree noted in these ten patients are described and analyzed.

3. Recognition of the variety of pressure pulses encountered, the location at which each is apt to occur, the variation caused by shift in the catheter position, and the phase and contour distortion seen in those which simulate ventricular pressure curves can help to reduce the incidence of inadvertent protracted catheterization of the coronary sinus and its tributaries.

4. Use of fluoroscopy in oblique positions and inspection of the color of the blood draining from the catheter have been emphasized as a means of verifying the suspicion of penetration of the catheter into the coronary sinus.

5. Because of the dangers involved in deep catheterization of the coronary venous tree, the importance of early recognition of catheterization of the coronary sinus is stressed.

We are indebted to the physicians of the several patients for permission to use their cases and to the members of the catheterization team for their assistance.

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***If need be, this was checked by fluoroscopy in the oblique positions and inspection of the blood drawn from the catheter.**

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TOXIC EFFECTS OF 1-HYDRAZINOPHTHALAZINE IN AMBULATORY HYPERTENSIVE PATIENTS

MAURICE H. WALD, M.D., MANUEL I. FIERRO, M.D.,* AND KENNETH H. KEETON, M.D.*

EVANSTON, ILL.

THE purpose of this report is to present our results with the administration of 1-hydrazinophthalazine (Apresoline)† to a selected group of ambulatory outpatient hypertensive individuals. Most published data have been concerned with studies of hospitalized hypertensive patients. Since the majority of hypertensives must be treated as ambulatory outpatients, we selected eleven cases of established hypertension of varying severity for study. In all instances their past clinical course was well known to us. Earlier work indicated that sustained hypotensive effects were difficult to maintain with this drug alone, so that most clinical data show the results of treatments combining Apresoline alternately with other alleged antihypertensive drugs.[1,2] In this study we have used Apresoline alone.

We were primarily interested in the effects of this substance upon blood pressure, upon the symptoms and signs of hypertension, possible acute and chronic toxicity and individual tolerance. Accordingly, only the pertinent clinical literature is included in the bibliography.[1-10]

METHODS

Twelve patients who had been followed in the Outpatient Clinic of the Evanston Hospital from 1 to 13 years were selected for this study. Of these, one who had asthma and angina pectoris developed severe substernal pain, slight nausea, headache and coldness, eight hours after taking a single dose of 25 mg. of Apresoline. No more drug was given and the case was not included in the series.

Table I gives a summary of the pertinent data on the eleven patients studied. The numbers correspond to those shown on Fig. 1 accompanying each blood pressure graph. That this was a rather typical group of ambulant hypertensive individuals is brought out by the following data: Nine had systolic blood pressure above 200 mm. Hg, and nine had diastolic pressure above 100 mm. Hg.

From the Renal-Hypertension Clinic and the Department of Medicine, Evanston Hospital Association, and the Department of Medicine of Northwestern University Medical School.

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*Residents in Medicine in the Evanston Hospital at the time of their participation in this study.

†Apresoline is the registered trade name for 1-hydrazinophthalazine manufactured by Ciba Pharmaceuticals Products, Inc., and supplied to us through the courtesy of Dr. Cornelius H. Sullivan.

There were nine women and two men of whom eight were Negroes and three were whites. Four were over 65 years of age, the remaining seven being 55 years or less. Two cases showed chronic congestive cardiac failure and three complained of angina. Retinopathy beyond the grade of simple spasm was seen in four. There was borderline impairment of renal function in two patients, but no cases of frank uremia were noted. Hypertensive encephalopathy of severe grade and healed myocardial infarct were present in patient No. 8.

TABLE I

CASE NUMBER	1	2	3	4	5	6	7	8	9	10	11
Cardiac											
Enlargement		3				3			2	2	
Angina		2						1		1	
Congest. failure				1		3	1			1	
ECG changes	1	2			1	3		4	1	2	
Healed infarct						+		+			
Renal											
Urine			1			1		2			
Nitro. retention	1					1		1			
Retinopathy	1	3	1	1		2	1	2	1	1	3
Serology	+		+				+				+
Anemia							1				1

Case numbers correspond to those identifying each blood pressure graph in Fig. 1. The degree of involvement resulting from the abnormality listed is graded from 1 to 4 according to severity. This is a tabulation of the significant pathology present in the patients at the time 1-hydrazinophthalazine was started.

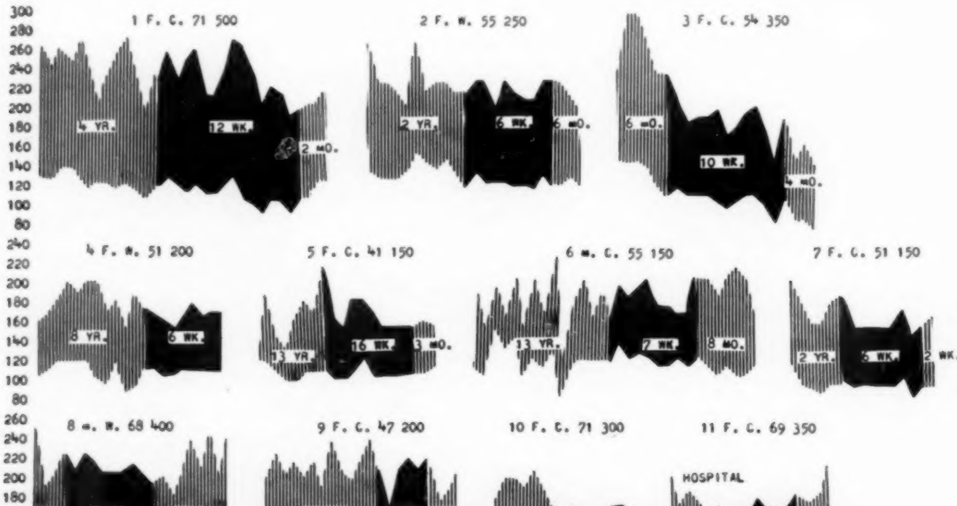

Fig. 1.—Blood pressure graphs of patients with numbers corresponding to the case numbers at the head of the columns on Table I. The solid black area shows the blood pressure during the administration of 1-hydrazinophthalazine. The duration of each period during which blood pressure was recorded is superimposed. Identifying each graph, the case number appears first. Following this in order are: sex (F—female, M—male), race (C—Negro, W—white), age in years, and the maximum tolerated daily dose of 1-hydrazinophthalazine expressed in milligrams.

The duration of therapy was from 4 to 16 weeks, and the drug dosage ranged from 150 to 500 mg. daily in divided quantities. Dosage was begun at 12.5 mg. three times daily (after our initial disquieting experience with the single 25 mg. dose noted above). This was gradually increased to the point of tolerance, that is the dosage level at which the patient experienced persistent or increasing severe toxic side effects. The usual division of dosage was either 3 or 4 times daily, whichever proved most effective. Every effort was made to encourage continuation of the drug when mild, toxic, early side reactions appeared.

The blood pressure was measured by one of us three times weekly during the first weeks of therapy and then once a week until discontinuance of the drug. Digitalis, low-sodium diet, and ammonium chloride were continued during the trial period in case No. 6, since he had been on this regimen for years. Aside from the continued use of phenobarbital in three cases and the occasional use of aspirin by others, no medication other than Apresoline was given.

RESULTS

Figure 1 graphically records the blood pressure responses of the patients. The numbers of the blood pressure graphs correspond to the patient numbers in Table I. Following the patient number the sex, race, age and maximum tolerated daily dosage of the drug are indicated. Of the eleven cases, only patients No. 3 and No. 10 may be considered to have achieved significant lowering of blood pressure. In the first instance, the patient is an aged Negro woman with hypertension of 18 years known duration, and in the second, a middle-aged Negro woman with what was apparently a rapidly developing hypertension of recent origin but of moderate grade. In all other cases, hypotensive effects noted during the period of therapy were not greater than could be accounted for by spontaneous fluctuation.

Eight of the eleven patients experienced toxic symptoms during therapy without relief of hypertensive symptoms where present. Two patients were relieved of hypertensive complaints and experienced mild toxicity. In one case there was no change in the subjective status except at the time maximum Apresoline dosage was reached. None of these patients tolerated a total daily dose of 1-hydrazinophthalazine in excess of 500 mg. although sustained total daily doses up to 900 mg. have been reported by Schroeder[1] and 1,400 mg. by Page.[5] Ultimately, three patients who took the drug from four to fourteen weeks refused to continue because of severe, persistent side effects.

The significant toxic side effects noted by us included: severe headache, faintness, dyspnea, anorexia, nausea, weakness, angina pectoris, paresthesia and epiphora.

No significant alterations of the patients' urinalysis, hemogram, electrocardiogram, ocular fundi, or gross cardiac dimensions were observed. No chronic toxicity was noted.

DISCUSSION

Of Schroeder's fifty cases treated with 1-hydrazinophthalazine alone,[1] thirty-five were hospital patients who were observed during a control period of one week immediately prior to the 10 to 30 day period of drug administration. Of the remaining fifteen patients who were treated as ambulatory outpatients over longer periods, three were totally unable to tolerate the drug and five others abandoned it after 2 to 10 weeks. It is stated that "no serious, chronic toxic manifestations" were encountered. Both Schroeder and Page are of the opinion that prolonged administration to outpatients is feasible. 99

Our over-all experience with the drug closely parallels that of Johnson and associates[2] who also found it necessary to increase the dosage slowly from very small initial levels because of rapid development of toxic effects. The maximum tolerated dosage in our series was 500 mg. daily.

Below a certain limiting dosage, each patient is usually able to tolerate gradually increasing dosages of the drug without appreciable increase in side effects. Where hypotensive effect occurs, steadily increasing dosages are required.

CONCLUSIONS

Of a characteristic group of eleven ambulatory hypertensive patients treated with 1-hydrazinophthalazine, one patient showed a marked hypotensive effect and another who had mild hypertension displayed an apparent modest reduction in blood pressure. Toxic side effects were observed in all, being fairly severe in eight and ultimately intolerable in three of these.

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ANTICOAGULANTS IN THE TREATMENT OF CARDIAC INFARCTION

A. J. Kerwin, M.D.

Toronto, Canada

THE evaluation of a method of therapy is frequently difficult unless immediate and dramatic benefits are achieved. This is particularly the case where the object of treatment is to prevent complications which are not easily predictable as to incidence, location, time of onset, and outcome. This situation is nowhere better exemplified than in the assessment of the effects of anticoagulants on the morbidity and mortality of cardiac infarction.

Though present knowledge of the process of thrombosis and of the influence of anticoagulants on it is far from complete, there are theoretical and experimental reasons for supposing that by their use the thrombotic complications of cardiac infarction can to some extent be avoided and that perhaps coronary thrombosis itself may be averted if opportunity presents. Experimental evidence has been advanced by Solandt and Best[1] and by Solandt and associates[2] which indicates that the "formation of mural thrombi may be completely prevented by he administration of adequate amounts of highly purified heparin."[2] Expense and the difficulties of administration have hindered the widespread use of heparin n cardiac infarction. Dale and Jaques[3] later showed that experimental thrombosis can also be prevented by Dicumarol. In 1946 several small series[4-6] of patients with myocardial infarct were treated with Dicumarol and the results suggested that this therapy might have value. The largest series is that of the American Heart Association reported by Wright[7] in which both the mortality rate and the frequency of thrombo-embolic complications were significantly reduced. In the papers of Glueck and associates,[8] Greisman and Marcus,[9] Hilton and associates,[10] Schilling,[11] Tulloch and Gilchrist,[12] Bresnick and associates,[13] and Smith and associates,[14] among others, a similar conclusion was reached. Some have challenged this conclusion. The difficulty is to decide to what extent complications may be prevented and to determine if there are special indications which will permit the selection of cases most likely to derive benefit. There is no dispute that thrombotic complications have a serious effect on the patients' chances of survival, but there is yet no general agreement as to their incidence. It is, therefore, not easy to evaluate the beneficial effects of anticoagulants. Since this treatment requires hospital supervision, is thereby expensive, and is not without danger, its value is an important problem to settle. Many physicians

From the Department of Medicine, the Toronto Western Hospital, and the University of Toronto.
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believe that the usefulness of anticoagulants in cardiac infarction is firmly established. Not all observers are convinced that their routine use is indicated. A recent editorial[15] pointed out that on superficial examination it would appear that anticoagulants are responsible for a decrease in the occurrence of thromboembolic complications and deaths. More detailed analysis, however, suggested that the incidence in treated series was not necessarily very different from that in some of the control series. Moreover the higher death rate in one control group[12] was due to preponderance of patients who probably could not have been saved by anticoagulants. Rytand[16] expressed the opinion that "there appears to be absolutely no valid evidence that prognosis for survival is improved by use of the drugs." Russek and associates[17] have recently reaffirmed his previous stand that the routine use of anticoagulant is neither necessary nor desirable. It is thus obvious that the case for the routine administration of thrombus-preventing substances in myocardial infarction is by no means conclusive.

The importance of having a clear picture of the natural course of myocardial infarction has been emphasized by several observers.[16,18-20] In spite of the publication of a number of large series treated for the most part only by supportive measures, the rates of death and of different complications vary greatly from author to author. These variations depend on the type of material available, the criteria used for the diagnosis, the care with which complications were looked for and other factors. Some criticism has been levelled at the practice of utilizing hospital patients as controls. Obviously this approach disregards those who die suddenly or very soon after the onset and also those who for various reasons are not admitted to a hospital. Certainly anticoagulants cannot be expected to help the former group. Some of the variation in results among different series is due to differences in the type of patient admitted to hospital but this factor is not easily susceptible of analysis. It seems legitimate to attempt to determine what benefit anticoagulants may have for the patient usually admitted to a hospital, using as controls the same type of case.

The need for an adequate group of controls in most biologic experiments is recognized. However, it is not always appreciated that the mere collection of such a group does not automatically guarantee that its characteristics will closely resemble those of the treated series in all respects except for the feature under investigation. The submission of results in two series to statistical tests in a search for significant differences is valid, but the usefulness of such tests is predicated on the assumption that the two samples are alike in every other way. There is no magic in a formula such as the chi-square test which will correct for differences in the composition of two series in addition to the characteristic under investigation. Hence, deductions from "statistically significant differences" are valid only if the basic data are properly drawn up.

It is recognized that women are less susceptible to coronary atherosclerosis and its sequelae than are men and tend to develop the disease at a later age. The sex composition of any series will have a bearing on the mortality since most authors report a higher mortality rate in women. The proportion of women in most series varies from 12.7 per cent[20] to 40.2 per cent[21] with the usual figure somewhere between 20 and 25 per cent.

The factor of age is also of great importance. The average age for both sexes ranges from 54 years[23] to 60.3 years,[11] the usual being about 60 years, slightly less for men and slightly more for women. However, averages mean nothing unless one takes account of the age distribution which has an important influence on the mortality rate and on the incidence of complications. This is one of the most obvious faults in small series such as that of Glueck and associates,[8] where of twenty-five control patients only five were less than 50 years old, while in the twenty-five treated patients no less than nine were in this group. If it is true that mortality rates are higher in the older patients,[19] Glueck's result was weighted in favor of the treated group from the start. Similar criticism might be directed at other reports if the authors had seen fit to set down the age composition of their series rather than merely to state that the controls were alike in respect to age. Doscher and Poindexter[19] have recently summarized the age distribution of several large groups in the literature. Table I shows the distribution of these groups as well as those of Billings and associates,[18] Doscher and Poindexter,[19] and Mintz and Katz[22] and the control series in this report. Collected data from several large "selected" groups such as these might well serve as a control in future investigations.

TABLE I. AGE DISTRIBUTION OF SERIES OF "UNTREATED" CARDIAC INFARCTION*

AUTHOR	<50 YEARS	50-59 YR.	60-69 YR.	70 YR. AND UP	TOTAL
Summarized by Doscher and Poindexter[19] (see Table II)	(%) 736 (24.8)	(%) 992 (33.2)	(%) 942 (31.6)	(%) 312 (10.4)	2982
Doscher and Poindexter[19] (see Table I)	107 (25.9)	161 (38.7)	112 (27.2)	34 (8.2)	414
Billings et al.[18]	43 (23.4)	44 (23.9)	55 (29.9)	42 (22.8)	184
Mintz and Katz[22]	113 (19.7)	187 (32.7)	192 (33.6)	80 (14.0)	572
This series (controls)	30 (18.8)	51 (31.8)	52 (32.5)	27 (16.9)	160
Total	1029 (23.9)	1435 (33.3)	1353 (31.4)	495 (11.4)	4312

*Where the age groups below 50 and above 70 years were subdivided in the original papers, they have been regrouped to conform to the above pattern.

Age and sex are undoubtedly important factors readily analyzed. There are others which are less easy to assess. Obesity might conceivably have an adverse influence but little attention has been paid to it. Tulloch and Gilchrist[12] mention that it was almost twice as common in the treated group. In some series (Smith and associates,[14] Billings and associates[18]), contrary to what one might expect, obesity seemed to have a favorable effect on the mortality rate. Even more neglected is the possibility that a family history of coronary disease might be significant. No large scale study of this phenomenon appears to have been undertaken.

Considerable attention has been paid to the patient's cardiac status before the attack. The incidence of previous cardiac infarcts varies greatly. Nay and Barnes[24] reported a 12 per cent incidence while Master and associates[23] showed a frequency of 47 per cent. The usual incidence seems to be between 15 and 20 per cent. Antecedent infarction adds to the seriousness of the outlook. Of 2,357 cases suffering from their first clinical attack (summarized by Doscher and Poindexter[19]) 18.3 per cent died. The mortality rate of second attacks in 533 cases was 30 per cent and of third attacks in 89 cases was 35.9 per cent. Similarly, angina is considered to affect the mortality rate unfavorably.[19]

The effect of the location of the infarct on the mortality rate has also claimed attention. The usual experience[14,18,19,22] is that anterior infarcts form about 55 to 60 per cent of any series and posterior infarcts about 40 to 45 per cent. There has been some dispute about their respective mortality rates. Many observers feel that anterior infarction carries a graver prognosis, some that posterior infarction is more serious. The truth is probably that there is no significant difference. When infarcts are difficult to localize accurately, it often means massive involvement and the mortality rate is much higher.

Hypertension varies in frequency from 35 to 70 per cent,[12,18,19,22,23] and is much more common in women. Some observers[19,25] indicate that it increases the mortality rate considerably, while others[18,22] claim that it does not affect prognosis. Since its incidence is much higher in women, if it does have a serious effect, an unusually high percentage of women in a series is likely to raise the fatality rate. It is generally agreed that the presence of failure is a bad omen. Diabetes appears not to alter the mortality rate.

One of the vexing problems is the question of thrombo-embolic complications because an accurate knowledge of their frequency in the natural course of "untreated" myocardial infarction is indispensable in deciding if anticoagulants should be used. There is no doubt that thrombosis is common in bed patients seriously ill from any cause. It is logical to assume that small thrombi often form and are dissipated again without becoming clinically manifest. Only if they happen to occur in a strategic site, or grow sufficiently large, or throw off emboli are they likely to attract the clinician's attention. Obviously autopsy will reveal a much higher incidence in fatal cases than will clinical or laboratory methods in series in which a large number have survived. It is reasonable to suppose that thrombotic phenomena are more common in fatal cases than in survivors. Hellerstein and Martin[26] summarized 1,605 cases of cardiac infarction from the literature and found the incidence of "clinically detectable thrombo-embolic lesions" to be 11.5 per cent. Contrast this with an incidence of 45 per cent in 160 autopsied cases.[25] In the fatal cases "thrombo-embolic complications were important as the cause of death" in 26.9 per cent. No doubt the detectable incidence at the bedside is lower than this in a series made up of both fatal and nonfatal cases. The figures in the literature vary from the 6.5 per cent of Doscher and Poindexter[19] to the 41.8 per cent of Wright.[7] A great deal depends on the care with which these complications are sought and on the criteria used in their diagnosis. The diagnosis will be relatively easy when an embolus involves organs such as the brain, mesentery, or limbs. But how should one interpret a patch of râles

at the lung base or a mild recurrence of chest pain without further unequivocal electrocardiographic changes?

Attempts have been made to divide cases on the basis of their severity. Russek and associates[20] showed in their series that in "good risks" thrombo-embolic complications occurred in less than 1 per cent but in "poor risks" in 7.7 per cent. A similar trend was noted by Papp and Smith.[27] While no one will deny that in general the more serious cases are prone to develop thrombosis, it is much easier to classify patients in this way in retrospect than it is to pick out such an individual in the first few days of illness when anticoagulant therapy should be started. Some of this criteria by which "poor risks" were selected have no very obvious relation to thrombosis. On the other hand the "unexpected" appearance of this complication in a patient who could up to then be considered a "good risk" is not rare in our experience. It is evident that if we are to be selective in our choice of cases for anticoagulant treatment, the usual clinical criteria of severity which have up to now been suggested are inadequate.

It is apparent from the above discussion that the picture of the natural course of cardiac infarction is not yet clear in all its details. Until careful analysis of many more cases is carried out, conclusions as to the value of any particular form of therapy can only be tentative.

MATERIAL

Because the preliminary reports on the treatment of cardiac infarction with Dicumarol were favorable, its use was begun in 1947. Under the circumstances no parallel control series could be set up. For the reasons noted previously, it was believed that a satisfactory control group could be drawn from the files of the same and the preceding years. No case was included in either group unless the recorded data were adequate. Because Dicumarol requires from one to three days to produce hypoprothrombinemia, its administration could not be expected to reduce the frequency of death or thrombo-embolism before three days had elapsed. Therefore, all cases who died within 72 hours of admission to hospital were excluded from both series.

If there were none of the generally accepted contraindications to anticoagulants, Dicumarol (and later Danilone (phenylindanedione)) was started at once, a dose of 300 mg. being given the first day and 200 mg. or 100 mg. the second. Subsequent dosages were designed to keep the prothrombin time (determined daily, including weekends) between 30 and 40 seconds. This regimen was continued usually for about four weeks, ideally until the patient had been out of bed for two days. Patients in which the prothrombin activity was not consistently depressed for at least three weeks were excluded from analysis. Sometimes medication was stopped before the three-week minimum was completed because of hemorrhage. Tromexan has been used in some cases (not reported here) but because of wide rapid fluctuations in prothrombin time, it was felt not to be as satisfactory as Dicumarol or Danilone. Tulloch and Gilchrist[28] and Scarrone and associates[29] on the other hand have reported favorably on the usefulness of Tromexan. Danilone became available in 1951 and was found to be preferable to Dicumarol because of the rapidity of its effect and its more consistent day-to-day dosage level.

Major hemorrhage was an indication to stop the anticoagulant. Vitamin K and rarely transfusion were employed when needed. Because hematuria is the most common manifestation of hemorrhage and gross hematuria is often preceded by microscopic bleeding, it was decided in August, 1949, to adopt the policy of having a daily benzidine test done on the urine. A positive test was not necessarily an indication to stop the drug since the test not infrequently became negative again, but it was regarded as a warning to exercise even more than the usual caution. In addition to these specific measures all cases were treated with at least three and usually four to five weeks of bed rest, sedatives, oxygen, digitalis, etc.

A total of 220 patients treated with Dicumarol was found suitable for analysis. A further group of 81 patients treated with Danilone was also analyzed. The results are tabulated separately, but there is no reason to suppose that a difference in the anticoagulant used affects the results and so the two groups have been combined in the final analysis.

RESULTS

In Tables II to VII are summarized the data on the control and treated series. For the most part, these have been analyzed in a fashion similar to that of Wright and associates.[30] Although those treated with Dicumarol and with Danilone have been shown separately and in combination, the discussion will concern itself with the treated cases as a whole.

In Table II the composition of control and treated cases is presented. The age and sex distribution and average ages were alike.

In Table III are shown the death rates of control and treated series. In the control group the mortality rate for all cases was 29.4 per cent which is slightly higher than the 26 per cent mortality rate of 808 control cases summarized by Brambel.[31] The rate for treated cases was distinctly less, 17.9 per cent, and similar to the 15 per cent death rate in 836 treated cases.[31] A slightly greater reduction of mortality rate was evident among the women.

In each of the four age groups fewer of the treated patients died, this reduction being most striking in those patients of 60 years and older and much less evident in those under 60. Wright and associates[30] also found that there was a greater reduction in mortality in patients over 60 years of age and distinctly less in the younger groups.

Table IV shows the breakdown of the data on deaths. In the first week the mortality rate in the treated group was actually a little higher than in the controls but thereafter it fell off though by no means consistently. In respect to the location of the infarct all three groups showed a fall in death rate. It is of interest to note that the proportion of cases in each location was almost identical in both series.

TABLE II

	NO. PATIENTS	MEN		WOMEN		AVERAGE IN YEARS			AGE DISTRIBUTION IN PER CENT			
		NO.	(%)	NO.	(%)	TOTAL	MEN	WOMEN	<50	50-59	60-69	70>
Treated—Dicumarol	220	167	75.9	53	24.1	58.8	57.7	62.4	19.1	34.5	32.3	14.1
Treated—Danilone	81	62	76.5	19	23.5	61.4	59.6	67.0	13.6	28.4	29.6	28.4
Treated—Total	301	229	76.1	72	23.9	59.5	58.2	63.7	17.6	32.9	31.6	17.9
Controls	160	122	76.3	38	23.7	58.8	57.6	62.3	18.8	31.8	32.5	16.9

TABLE III

	CASES	TOTAL DEATHS		MEN		WOMEN		MORTALITY RATE (%) BY AGE			
	NO.	NO.	(%)	NO.	(%)	NO.	(%)	<50	50-59	60-69	70>
Treated—Dicumarol	220	39	17.7	29	17.4	10	18.9	9.5	17.1	22.5	19.4
Treated—Danilone	81	15	18.5	13	20.9	2	10.5	18.2	17.8	16.7	21.7
Treated—Total	301	54	17.9	42	18.3	12	16.7	11.3	17.2	21.1	20.6
Controls	160	47	29.4	35	28.7	12	31.6	16.6	19.6	30.8	59.3

TABLE IV

	DEATHS BY WEEK OF ILLNESS—% OF SURVIVORS FROM PREVIOUS WEEK							LOCATION OF INFARCT						PREVIOUS ANGINA OR INFARCT*	
								ANTERIOR		POSTERIOR		OTHER			
	1	2	3	4	5	6	OTHER	NO.	DEATHS	NO.	DEATHS	NO.	DEATHS	NO.	DEATHS
Treated with Dicumarol—220 cases	2.7	6.5	4.0	2.6	2.1	0.6	0.6	123	23	88	15	9	1	91	19
Treated with Danilone—81 cases	9.9	2.8	4.2	1.5	0	1.5	0	48	5	27	7	6	3	35	7
Total treated with Anti-coagulants—301 cases	4.6	5.6	4.0	2.2	1.5	0.7	0.7	171 56.8%	28 16.4%	115 38.2%	22 19.1%	15 5.0%	4 26.7%	126 47.9%	26 20.5%
Control Series—160 cases	3.1	11.4	6.1	3.2	0.9	1.7	3.4	89 55.6%	26 29.2%	64 40.0%	16 25.0%	7 4.4%	5 71.1%	40 32.0%	12 30.0%

TABLE IV. (CONTINUED)

	NO PREVIOUS ANGINA OR INFARCT		HYPERTENSIVES		NON-HYPERTENSIVES		DIABETICS		FAILURE			
									PRESENT		ABSENT	
	NO.	DEATHS	NO.	DEATHS	NO.	DEATHS	NO.	DEATHS	NO.	DEATHS	NO.	DEATHS
Treated with Dicumarol—220 cases	91	14	65	15	155	24	18	3	70	25	150	13
Treated with Danilone—81 cases	46	8	18	4	63	7	5	0	35	10	46	5
Total treated with Anti-coagulants—301 cases	137 50.7%	22 15.7%	83 27.6%	19 22.9%	218 79.4%	31 14.2%	23 7.6%	3 13.0%	105 34.9%	35 33.3%	196 65.1%	18 9.2%
Control Series—160 cases	85 68.0%	22 25.9%	63 39.4%	15 23.8%	97 60.6%	32 32.9%	15 9.4%	5 33.3%	63 39.4%	38 60.6%	97 60.6%	9 9.3%

***Cases in which satisfactory data were available: controls 125, treated with Dicumarol 182, treated with Danilone 81, total treated with anticoagulants 263.**

TABLE V. THROMBO-EMBOLIC PHENOMENA (TEP)

	DEATHS		NO. OF CASES			AVERAGE AGE IN YEARS			NO. OF COMPLICATIONS	COMPLICATIONS BY AGE GROUPS			
	PRECEDED BY TEP	NOT PRECEDED BY TEP	TOTAL	MEN	WOMEN	TOTAL	MEN	WOMEN		<50	50-59	60-69	70+
Treated with Dicumarol—220 cases	9	30	17	4	3	57.3	55.0	68.3	19	4	5	5	3
Treated with Danilone—81 cases	6	9	6	6	0	58.5	58.5	—	6	2	1	2	1
Total treated with anti-coagulants—301 cases	15 4.9%	39 12.9%	23 7.6%	20 8.6%	3 4.2%	57.6	56.0	68.3	25 8.3%	6 11.3%	6 6.1%	7 7.4%	4 7.4%
Control Series—160 cases	16 11.9%	31 17.5%	32 20.0%	24 19.7%	8 21.1%	61.7	60.5	65.3	36 22.5%	4 13.3%	10 19.6%	13 25.0%	9 33.3%

TABLE V. (CONTINUED)

	COMPLICATIONS BY WEEK OF ILLNESS* (% OF SURVIVORS FROM PREVIOUS WEEK)						TYPE OF COMPLICATION			
	1	2	3	4	5	6	RECURRENCE	VEN. THR. AND PUL. EMB.	CEREB. EMB.	PERIPH. EMB.
Treated with Dicumarol—220 cases	8	4	4	1	0	2	10	6	3	0
Treated with Danilone—81 cases	4	0	1	1	0	0	6	0	0	0
Total treated with Anticoagulants—301 cases	12 4.0%	4 1.4%	5 1.8%	2 0.8%	0 0	2 0.8%	16 5.3%	6 2.0%	3 1.0%	0 0
Control Series—160 cases	10 6.3%	3 2.0%	6 4.5%	6 4.8%	4 3.3%	4 3.4%	20 12.5%	7 4.4%	6 3.8%	3 1.9%

*In the controls 3 complications occurred after the sixth week and in the treated cases none.

More patients with previous evidence of coronary disease (47.9 per cent) were found in the treated than in the control series (32.0 per cent). The reduction in mortality rate of about 10 per cent might have been greater otherwise, since previous angina or infarction is recognized to impair chances for survival. In hypertensive patients the death rate in the controls was somewhat greater than that in the normotensives. In the treated hypertensives no decrease in the number of fatalities was found but in the treated normotensives the rate was less than one-half. The proportion of diabetic patients was about the same in both groups but deaths were much fewer among the treated. As might be expected, the death rate in the control group in failure was much greater (six times) than that of patients without failure. An interesting observation is the fact that all the reduction in mortality in the treated groups occurred in those with failure and there was no decrease in those without failure.

There was a decrease in the number of deaths preceded by thrombo-embolism from 11.9 per cent in the control series to 4.9 per cent in the treated group (Table V). Interestingly enough, deaths not so preceded were also fewer, 12.9 per cent in the treated cases compared with 17.5 per cent in the control cases. This could conceivably be due to the fact that there must be some deaths due to unrecognized thrombo-embolism in the "not preceded" group in both series and that anticoagulants have been of some benefit in the treated group. In Table V is shown the decrease in the frequency of thrombotic complications from 20.0 per cent in the controls to 7.6 per cent with anticoagulants. A somewhat greater reduction was noted for women as compared with men. The average age of the treated men developing these complications was four and one-half years less than that of the controls. The significance of this, if any, is obscure. There were too few women to justify analysis. The total number of thrombotic complications fell from 22.5 to 8.3 per cent.

In the three older age groups there was a marked reduction in the frequency of thrombosis, but there was little difference in those under 50 years of age; however, the numbers were too small for any conclusion to be drawn. Except for the first week these complications in the control group were more or less evenly apportioned throughout the succeeding weeks. There were somewhat fewer cases in the first two weeks under treatment but the greatest decline occurred after this time. Wright and associates,[30] on the contrary, found that there was a considerable advantage in anticoagulants even in the first fortnight. All types of thrombotic complication were less common in those treated with anticoagulants (Table V).

An attempt was made (Table VI) to see what effect the presence of both cardiac failure and previously recognized coronary disease, as evidenced by a history of angina and/or infarction, would have on the mortality rate and the frequency of thrombo-embolic phenomena. Eighty-seven controls and 263 cases treated with anticoagulants were analyzed and the incidence of these two factors combined was about the same in the two series. As expected, in the controls the mortality rate was about doubled compared with this group as a whole and a

similar difference was noted in the treated cases. In the treated group the mortality rate was approximately one-half that of the control group. In those receiving anticoagulants, the frequency of thrombo-embolic complications was about one-third of that in the controls but not significantly different from the treated series as a whole.

TABLE VI. EFFECT OF CARDIAC FAILURE AND HISTORY OF PREVIOUS CORONARY DISEASE IN THE SAME PATIENT ON MORTALITY RATE AND FREQUENCY OF THROMBO-EMBOLIC PHENOMENA

	CONTROLS	TREATED
No. of cases analyzed	87	263
No. with failure and previous coronary disease	(%) 15 (17.3)	(%) 52 (19.8)
No. of deaths	9 (60.0)	16 (30.8)
No. with thrombo-embolism	5 (33.3)	6 (11.5)

In the control group no data were available as to the incidence of hemorrhage (Table VII). In the treated series there were 263 cases in which daily examination of the urine for blood was done. Hemorrhagic complications occurred in 18.6 per cent, largely from the urinary tract. Many of these showed only a positive chemical test for blood and treatment was not stopped on this account because the bleeding often ceased although the hypoprothrombinemia was maintained.

It is interesting to note that bleeding was much less common with Danilone than with Dicumarol. A similar low incidence of hemorrhage with Danilone has been reported by Preston and associates.[32] No deaths attributable to anticoagulants occurred in this series.

TABLE VII. HEMORRHAGIC COMPLICATIONS IN TREATED CASES

	NO.	(%)	HEMATURIA	EPISTAXIS	SKIN	GASTROINTESTINAL	HEMOPTYSIS	OTHERS
Treated with Dicumarol*—182 cases	43	19.5	31	5	3	2	1	1
Treated with Danilone—81 cases	6	7.4	1	0	1	4	0	0
Total treated with anticoagulants—263 cases	49	18.6	32	5	4	6	1	1

*Of the 220 cases so treated, 182 had daily urine examination for blood.

DISCUSSION

It is generally agreed that, while clotting and thrombosis are closely related processes, they are not identical. Nonetheless, it is known that thrombosis can be minimized or prevented by modifying one of the factors in the clotting mechanism, i.e., prothrombin. The exhibition of certain anticoagulants inhibits the formation of prothrombin and hence the development of both clot and thrombus. There is clinical evidence to suggest that hypoprothrombinemia (at least at the therapeutically desirable levels measured by the in vitro test) does not absolutely preclude thrombus formation where local conditions are suitable. Such an assumption helps to account for the occurrence of thrombo-embolic phenomena even after a reasonable period of anticoagulant treatment. There is another reason for expecting somewhat less than perfect results from such therapy. There is no doubt that thrombosis may begin early, before anticoagulants have had time to become effective. Many of the complications, particularly embolism, occurring in the first week or even later, can be so explained.

It is, therefore, obvious that routine anticoagulant therapy cannot be expected to abolish thrombo-embolism. The questions to be answered are the following: (1) To what extent may thrombo-embolic complications be prevented? (2) Are there types of cases ("poor risks") in which thrombosis is particularly likely to occur and how can they be identified? (3) Can all other cases ("good risks") safely be denied this therapy? (4) Do the dangers, expense, and inconveniences of anticoagulant therapy outweigh the advantages? We do not believe that a categorial answer can be given to these questions at present.

Since it is clear that thrombosis cannot wholly be prevented, it is essential to determine to what extent the situation can be improved by anticoagulants. This implies that one must have an accurate picture of its incidence in the natural course of the illness. In spite of a number of painstaking efforts to present such a picture, we cannot yet predict with assurance the frequency and sites of origin and lodgment of thrombi and emboli. If a purely clinical approach is used, many small and some large thrombi or emboli will be missed. If autopsy material is utilized, the incidence of thrombo-embolism will certainly be higher than in the patients seen at the bedside. Even at autopsy some thrombi will be overlooked because of the limitations in the extent of exploration. Evidence of arterial occlusion is discovered far more often anatomically than it is clinically. Thus Miller and associates[33] found arterial occlusion in 25 per cent of 210 cases of infarction. Hence, it is plain that neither clinical nor post-mortem data can give us a true appreciation of thrombo-embolic complications. Among cases of all types, it is commoner than clinical figures suggest but probably less frequent than autopsy shows. Until such time as accurate figures become available, it will be necessary to use such clinical control data as we can obtain, realizing full well their shortcomings.

Some attempt has been made to determine the type of case ("poor risk") in which anticoagulants are indicated. Russek and associates[17] have set forth criteria by which a "poor risk" is separated from a "good risk" group. Not all of these criteria have any obvious direct influence on thrombosis and some appear

to be only part of the picture of a seriously ill cardiac patient. No data have been presented to indicate just how important an individual criterion may be, and no doubt this would be very difficult to do in such a complex illness. Our figures confirm the idea that cardiac failure is indeed a serious sign since the mortality rate in the controls with this complication was 60.3 per cent. Coincidentally and perhaps as a result of the administration of anticoagulants, the rate fell to 33.3 per cent. The improvement in mortality rate was about the same for those with clinical evidence of previous coronary disease as for those without.

An attempt has been made to show the effect of anticoagulant treatment on those patients who had both myocardial failure during the acute episode and a previous history of angina and/or infarction. The percentage of cases so affected was about the same in control and treated series but the mortality rate of the treated was only one-half that of the controls while the incidence of thrombo-embolism was only one-third. Other factors in the "poor risk" group mentioned by Russek and associates[17] were not analyzed. No doubt combinations of other unfavorable signs would show a worse prognosis, but adequate analysis would require a very large series.

Whether or not "good risk" patients can be adequately handled without anticoagulants cannot be answered. Russek and associates[17] believe they can, but everyone has seen cases who would be so classified and who nevertheless developed thrombosis.

It is undeniable that to interfere with clotting is to run the risk of serious or fatal hemorrhage. Major bleeding may occur with a prothrombin time under 30 seconds but is often absent with a prothrombin time of several minutes. Excessive depression of prothrombin can largely be prevented by careful management, but inevitably there will occasionally occur a severe or even fatal hemorrhage.

Even if it is conceded that anticoagulant therapy is indicated in certain cases, there remains the problem of the method of administration and the choice of drug. It is believed that a prothrombin time consistently between 30 and 40 seconds is sufficient to prevent most thromboses but there is yet no concrete evidence to prove that this is the best level. More marked depression of prothrombin is all too easily achieved, but the risk of hemorrhage is greatly increased. It is conceivable that a prothrombin time between 20 and 30 seconds might be effective. In the only series[13] reported in which the levels were presumably in this range, Dicumarol failed to improve the mortality rate. This may have been due in part to "inconsistent maintenance of therapeutic levels." The importance of this factor is unknown. It might be argued that the inadvertent return of the prothrombin time to nearly normal for a period of only 12 to 24 hours does not result in thrombosis. But we are ignorant of the length of time necessary for thrombus formation under natural conditions and, therefore, it seems preferable to maintain a consistent and adequate blood level. In our experience this is easier with Danilone than with Dicumarol or Tromexan. A daily graphic record of the prothrombin time and anticoagulant dosage is an invaluable visual aid in estimating the required dosage and much to be preferred to any rule-of-thumb, however ingenious.

Because the manifestations of thrombo-embolism (though not necessarily their inception) may become evident as late as the sixth week or even later, one has to decide how long anticoagulant therapy should be continued. More or less empirically three weeks has been considered as the minimum desirable period. In our opinion this is too short and treatment should be carried on until the patient has been ambulatory for several days, i.e., five weeks in the average case. Inevitably some thrombi will occur after this time, but they may be regarded as evidence of the general tendency to thrombosis exhibited by these patients rather than as a complication of the original infarction. The problem of continuous and indefinitely prolonged therapy after infarction is not within the scope of this paper but the difficulties of maintaining adequately low but safe levels of prothrombin under any but ideal conditions prohibit its use in most patients.

SUMMARY

1. Theoretical and experimental considerations suggest that the use of anticoagulants in cardiac infarction will result in a reduction in the frequency of thrombo-embolic complications and a decline in the mortality rate. The results in most reported series appear to indicate that this therapy is definitely of value; however, several authors dissent. They claim that the routine use of anticoagulants in all cases is unnecessary because of the slight over-all benefit obtained, the expense and the risk, and that they should be employed only where the patient is a "poor risk."

2. In this series 220 cases of cardiac infarction were treated with Dicumarol and 81 cases with Danilone, a total of 301 cases. The control series was made up of 160 cases, comparable in age and sex distribution.

3. The mortality rate in the control series was 29.4 per cent and in the treated 17.9 per cent. The most marked difference was in patients over 60 years of age. The greatest reduction took place after the first week of therapy.

4. Where previous evidence of coronary disease (angina and/or infarction) existed, the mortality in controls was 30.0 per cent and in treated 20.5 per cent. Where no such diagnosis had been made before, the mortality rates were 25.9 per cent and 15.7 per cent, respectively. The mortality rate in hypertensives was not affected by treatment, but in nonhypertensives it was 32.9 per cent in the controls and 14.2 per cent in the treated. Diabetic patients showed a much improved death rate with anticoagulants, but the number of cases available was small.

5. In those patients who had no cardiac failure there was no difference in the death rate among treated and untreated patients. In the presence of failure, anticoagulant therapy was associated with a decrease in the death rate from 60.6 per cent (controls) to 33.3 per cent (treated). A similar reduction was evident in those cases who had both failure and previous coronary disease (60.0 per cent and 30.8 per cent, respectively). The deaths preceded by thrombo-embolic phenomena were fewer in the treated series (4.9 per cent) compared with the controls (11.9 per cent).

6. Thrombo-embolic complications occurred in 20.0 per cent of the controls and in 7.6 per cent of those receiving anticoagulants. A similar marked reduction in the total number of such complications was noted. These differences were evident only in patients over 50 years of age and were marked mainly after the second week of treatment.

7. In those treated with anticoagulants hemorrhagic complications, mostly in the urinary tract, occurred in 18.6 per cent. Bleeding was much less common with Danilone than with Dicumarol. No deaths due to hemorrhage occurred in the cases included in this series.

CONCLUSIONS

1. The natural course of patients with cardiac infarction is by no means yet clearly established, particularly in regard to such details as the frequency and distribution of thrombo-embolic phenomena. This fact makes the evaluation of therapy difficult.

2. Controversy has arisen as to whether anticoagulant treatment actually does reduce morbidity and mortality rates. There is also a difference of opinion whether all patients should be routinely so treated, or whether only complicated cases ("poor risks") require anticoagulants.

3. The present study cannot claim to settle these questions. The results suggest that anticoagulant therapy does influence the outcome favorably, most strikingly in patients with cardiac failure, especially in the older age groups.

4. Further intensive and carefully controlled studies are warranted.

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EFFECTS OF THIAMIN DEFICIENCY ON MYOCARDIAL METABOLISM IN INTACT DOGS

Donald B. Hackel, M.D., Walter T. Goodale, M.D., and Jerome Kleinerman, M.D.

Cleveland, Ohio

Numerous clinical studies have demonstrated the cardiodynamic changes that occur in "beriberi" heart disease.[1] It has been postulated that these changes are due, at least in part, to a metabolic defect which limits the utilization of carbohydrate by the myocardium. Since thiamin is known to catalyze the decarboxylation of pyruvate, it is likely that a deficiency of thiamin would result in defective utilization of carbohydrate. In a previous communication the importance of lactate, pyruvate, and glucose as sources of myocardial energy was demonstrated in normal dogs.[2] The present report concerns the findings in thiamin deficiency.

METHODS

The femoral artery, pulmonary artery, and coronary sinus were catheterized in intact lightly Nembutalized dogs by the technique described in a previous report.[3] The same methods and calculations were used as described in the preceding two papers in this series[2,3] in determining the left ventricular coronary blood flow, work, efficiency, utilization of oxygen, glucose, lactate and pyruvate, the cardiac output, myocardial respiratory quotient and total body oxygen consumption.

The usual dose of intravenous Nembutal for normal dogs is 25 mg./kg. The thiamin deficient dogs, however, required only one-third to one-half as much Nembutal to reach the same degree of anesthesia. This sensitivity to barbiturates may be related to the high arterial lactate level in the thiamin-deficient dogs, for Lamson has found that injection of sodium lactate resulted in a marked decrease in the anesthetic dosage of hexobarbital in guinea pigs.[4]

Thiamin deficiency was produced in adult dogs by feeding them a diet of canned dog food which had been autoclaved at 15 pounds pressure for 12 hours to destroy thiamin. This diet was supplemented by 200 mg. of ascorbic acid

From the Department of Pathology, Western Reserve University School of Medicine at City Hospital, Cleveland, Ohio; the Department of Medicine, Peter Bent Brigham Hospital, Harvard Medical School, Boston, Mass.; and the Chemical Corps, U. S. Army, Washington 25, D. C.

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given orally every two weeks, plus the following vitamins given orally three times a week: riboflavin, 3 mg.; niacin, 60 mg.; pyridoxine, 6 mg.; pantothenic acid, 15 mg.; choline, 300 mg.; inositol, 9 mg.; and para-aminobenzoic acid, 9 mg. The weights and food intake of these dogs were followed, and they were closely watched for the development of signs of thiamin deficiency. No evidence of myocardial failure was observed. In a series of six unanesthetized dogs the electrocardiograms were taken and, in four of these dogs, venous pyruvate levels were determined once a week during the development of thiamin deficiency. Studies of cardiac function were performed as outlined above in seven dogs after definite neurologic signs of acute thiamin deficiency had appeared. This occurred within an average of 51 days, and included an initial ataxia that began as awkwardness of the hind legs. It progressed to generalized muscular rigidity with opisthotonus, and finally to severe tonic-clonic convulsions. The convulsions ended in death unless thiamin was immediately administered. In three dogs that developed convulsions, complete relief was obtained within a few minutes by the intravenous injection of 10 mg. of crystalline thiamin. At the time the cardiac function studies were performed the dogs had lost an average of 32 per cent of their body weight. In most cases control studies were carried out on the same dog before the production of the deficiency. An additional three dogs were put on exactly the same regime as the above dogs, except that 6 mg. of thiamin were added to the thrice weekly vitamin supplement. They were maintained on this diet for one, four, and six months.

Chronic thiamin deficiency was produced in five dogs by supplementing the above diet with the minimum amount of thiamin, given by daily intramuscular injections five times a week, to prevent all signs of thiamin deficiency. This thiamin amount was found to vary between 50 and 100 micrograms. Body weight was followed, electrocardiograms taken, and venous pyruvate determinations were performed at various intervals for six to ten months. Metabolic studies by venous catheterization were carried out on three of these dogs when normal and after six to eight months of the chronic thiamin-deficient regime.

The following evidence is presented as proof that a specific thiamin deficiency was produced: (1) Dogs placed on the thiamin-deficient diet developed the characteristic signs of thiamin deficiency. (2) These signs were rapidly cured by the intravenous injection of small amounts of crystalline thiamin. (3) They were completely prevented up to six months in dogs who were kept on the same diet but were given supplementary thiamin in large amounts. (4) In five dogs who were kept without symptoms on a minimum daily dose of thiamin, small subtractions from the daily dose of thiamin were reflected in prompt weight losses which were quickly regained when the thiamin was again increased. (5) A progressive increase in the blood pyruvate level occurred during the course of the deficiency.

In the previous two papers in this series[2,3] the hemodynamic and metabolic findings in a series of twenty-two normal and four starved dogs were presented. These dogs were studied by exactly the same methods and at the same period of time as the thiamin-deficient dogs. Inanition was produced in the four dogs by withdrawing food so that their weights fell in parallel fashion to the thiamin-

deficient dogs, and they were given similar vitamin supplements plus 10 mg. thiamin three times a week. The mean findings in these two groups are therefore included in the tables and graphs in this paper to compare with the thiamin-deficient dogs.

RESULTS

A. Carbohydrate Metabolism

1. *Acute Thiamin Deficiency.*—Table I presents the detailed experimental data for the seven dogs with acute thiamin deficiency. In Table II the mean values for this series are compared with the findings in the twenty-two normal and the four starvation controls.

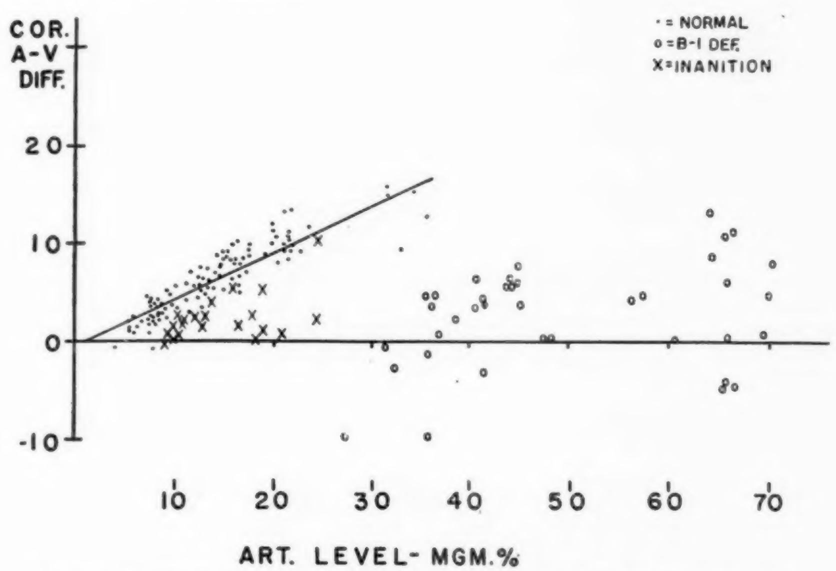

Fig. 1.—Relation of coronary arteriovenous differences to arterial levels of lactate.

The mean arterial lactate level in the thiamin-deficient dogs is markedly increased. The arteriovenous difference is significantly lower than that for the normal dogs but is not different from that of the starvation controls. The coefficient of extraction (A-V/A)* for lactate, however, is significantly lower than that for either control group. This relationship is brought out more clearly in Fig. 1, where the coronary arteriovenous differences for lactate are plotted against the simultaneously determined arterial levels. As has been demonstrated previously,[2] the normal series shows a straight line relationship between the two factors, with a high coefficient of correlation ($r = .89$) and a low threshold of utilization. The starved group shows values that are not far off this line, but the thiamin-deficient dogs have values which are shifted far to the right with an elevation of the threshold of utilization to the very high arterial level of 35 mg. per cent. The total left ventricular lactate utilization is less in the thiamin-deficient group than in the normal controls, but not much different from a similarly low value for the starved dogs.

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*A — V/A(%) = coronary arteriovenous difference × 100 ÷ arterial level.

TABLE I. SUMMARY OF ACUTE ATHIAMINOSIS EXPERIMENTS

	DOG NO.			57	67	T-3	T-2	T-5[1]	T-5[2]	T-9	T-7
	BODY WT. (KG.)			12.3	15.9	11.6	14.1	12.3	12.3	13.7	19.1
	L.V. WT. (GM.)	MEAN	$\pm \sigma_M$	94	90	88	83	80	80	82	94
LACTATE	Art.	51.7	5.0	64.7	38.9	39.0	34.8	56.3	65.7	44.0	70.5
	A-V	1.5	1.5	7.3	1.0	1.1	2.0	−4.2	−4.3	4.0	5.0
	C. Ext. (%)	3.1	2.3	11.6	2.6	2.8	5.7	−7.5	−6.5	9.1	7.1
	Util.	−0.4	2.4	6.6	0.9	1.4	2.1	−8.4	−9.9	—	4.5
PYRUVATE	Art.	5.54	0.46	5.75	5.39	4.04	4.51	6.38	8.04	5.80	4.41
	A-V	1.07	0.22	1.30	1.51	0.38	0.83	0.87	2.17	0.31	1.20
	C. Ext. (%)	18.9	3.1	22.6	28.0	9.4	18.3	13.6	27.0	5.3	27.2
	Util.	1.66	0.58	1.17	1.28	0.49	0.87	1.74	5.0	—	1.08
GLUCOSE	Art.	72.6	6.5	42	74	64	55	92	88	93	73
	A-V	0.8	0.8	−3.6	1.3	2.0	1.3	0	0	4.5	1.0
	C. Ext. (%)	0.6	1.3	−8.6	1.8	3.1	2.4	0	0	4.9	1.4
	Util.	0.4	0.7	−3.2	1.1	2.6	1.4	0	0	—	0.9
OXYGEN	Art.	19.0	1.0	21.9	18.5	15.1	14.7	21.2	18.4	21.5	20.5
	A-V	12.6	1.7	17.0	13.7	7.8	8.8	9.4	7.5	19.0	17.6
	C. Ext. (%)	65.2	6.6	77	74	52	60	44	41	88	86
	Util.	14.0	1.4	15.3	11.6	10.1	9.2	18.8	17.2	—	15.8

Cor. Flow	132.9	22.2	90	85	130	105	200	230	—	90
Art. B.P.	102.4	5.7	140	93	88	96	96	98	100	108
C. I.	4.5	0.5	5.0	2.7	5.0	5.7	—	5.1	—	3.3
L. V. Work	4.0	0.4	5.6	2.5	3.4	4.8	—	4.0	—	3.8
L. V. Effic. (%)	17.8	3.0	18	12	18	32	—	14	—	13
B. O. C.	165.2	11.7	193	136	189	131	—	190	—	152
Pulse Rate	178.5	8.1	180	188	168	130	187	177	210	188
P. A. R.	1.70	0.18	2.30	2.04	1.35	1.15	—	1.46	—	1.92
C. V. R.	54.4	9.3	93.3	65.5	40.6	54.8	28.8	25.6	—	72.0
Lact/Pyruv	9.5	1.0	11.2	7.2	9.7	7.7	8.8	8.2	7.6	15.9
Myoc. R. Q.	0.79	0.04	0.96	0.80	0.90	0.70	0.59	0.88	0.77	0.74

Art. = arterial (mg. % or vol. %); A-V = coronary arteriovenous difference (mg. % or vol. %); B.O.C. = total body oxygen consumption (c.c./square meter body surface area/minute); B.P. = blood pressure (mm.Hg.); C. Ext. = myocardial coefficient of extraction, i.e., A-V/A (%); C.I. = cardiac index (liters/square meter/minute); C.V.R. = coronary vascular resistance (arbitrary units); σm = deviation of mean; Lact/Pyruv = arterial lactate divided by arterial pyruvate; L. V. = left ventricle; P. A. R. = peripheral arteriolar resistance (arbitrary units); Util. = left ventricular utilization (mg. or c.c./100 Gm. of left ventricle/minute).

Note: Each value for glucose, lactate and pyruvate represents the average of 3 or 4 consecutively drawn blood samples.

Table II. Comparison of Mean Values in Athiaminosis and Control Series

		1. Athiaminosis			2. Normal			3. Starvation			P-1 1 and 2	P-2 1 and 3	P-3 2 and 3
		No. Obs.	Mean	$\pm \sigma_M$	No. Obs.	Mean	$\pm \sigma_M$	No. Obs.	Mean	$\pm \sigma_M$			
Lactate	Art.	8	51.7	5.0	68	13.3	0.6	11	15.5	1.4	<0.0001	<0.0001	0.2
	A-V	8	1.5	1.5	68	5.8	0.4	11	1.8	0.5	0.025	0.8	<0.0001
	C. Ext. %	8	3.1	2.3	68	41.1	1.7	11	13.6	2.9	<0.0001	0<.02	<0.0001
	Util.	7	−0.4	2.4	19	7.8	1.29	3	2.6	NSQ	0.015	NSQ	NSQ
Pyruvate	Art.	8	5.54	0.46	69	1.91	0.08	11	2.62	0.25	<.0001	0.0005	0.025
	A-V	8	1.07	0.22	69	0.88	0.06	11	0.21	0.07	0.5	0.007	<0.0001
	C. Ext. %	8	18.9	3.1	69	43.0	2.0	11	1.3	0.82	<0.001	0.0006	<0.0001
	Util.	7	1.66	0.58	19	1.13	0.18	3	0.30	NSQ	0.4	NSQ	NSQ
Glucose	Art.	8	72.6	6.5	66	75.8	1.8	12	66.0	3.3	0.6	0.4	0.5
	A-V	8	0.8	0.8	66	4.6	0.7	12	−1.0	0.5	0.008	0.1	0.0002
	C. Ext. %	8	0.6	1.3	66	5.7	0.9	12	−1.3	0.7	<.01	>0.2	<0.001
	Util.	7	0.4	0.7	16	12.2	2.5	3	−1.4	NSQ	0.002	NSQ	NSQ
Oxygen	Art.	8	19.0	1.0	33	17.4	0.4	3	19.8	NSQ	0.12	NSQ	NSQ
	A-V	8	12.6	1.7	33	12.9	0.4	3	15.2	NSQ	0.9	NSQ	NSQ
	C. Ext. %	8	65.2	6.6	33	74.1	1.4	3	76.8	NSQ	0.8	NSQ	NSQ
	Util.	7	14.0	1.4	33	19.5	1.5	3	20.9	NSQ	0.03	NSQ	NSQ

Cor. Flow	7	132.9	22.2	12	147.1	11.3	3	142	NSQ	0.6	NSQ	NSQ
Art. B. P.	8	102.4	5.7	12	145.1	3.7	3	120	NSQ	<0.0001	NSQ	NSQ
C. I.	6	4.5	0.5	12	4.5	0.24	3	6.1	NSQ	>1.0	NSQ	NSQ
L. V. Work	6	4.0	0.4	12	8.1	0.58	3	8.8	NSQ	<0.001	NSQ	NSQ
L. V. Effic. %	6	17.8	3.0	12	22.3	1.7	3	16	NSQ	0.2	NSQ	NSQ
B. O. C.	6	165.2	11.7	12	179.7	12.3	3	144	NSQ	0.4	NSQ	NSQ
Pulse Rate	8	178.5	8.1	12	158.2	5.1	3	165	NSQ	0.07	NSQ	NSQ
P. A. R.	6	1.70	0.18	12	1.88	0.16	3	1.15	NSQ	0.02	NSQ	NSQ
C. V. R.	7	54.4	9.3	12	62.6	4.5	3	55.4	NSQ	0.5	NSQ	NSQ
Lact/Pyruv	8	9.5	1.0	21	9.3	0.5	4	5.7	NSQ	0.9	NSQ	NSQ
Myoc. R. Q.	8	0.79	0.04	12	0.88	0.04	3	0.68	NSQ	0.15	NSQ	NSQ

Abbreviations. See Table I. NSQ = data insufficient for statistical analysis. P is probability that a difference between the 2 means as large or larger than that observed could occur by chance. When P <0.05 a significant difference between the means is considered to exist. (P–1 = athiaminosis and normal; P–2 = athiaminosis and starvation; P–3 = normal and starvation).

The threshold of utilization of pyruvate is also elevated in acute thiamin deficiency, and there is a reduced coefficient of extraction of pyruvate. In contrast to lactate, a normal mean pyruvate arteriovenous difference and total utilization are maintained, but only in the face of the elevated arterial level. These findings in thiamin deficiency are significantly different from those in simple starvation.

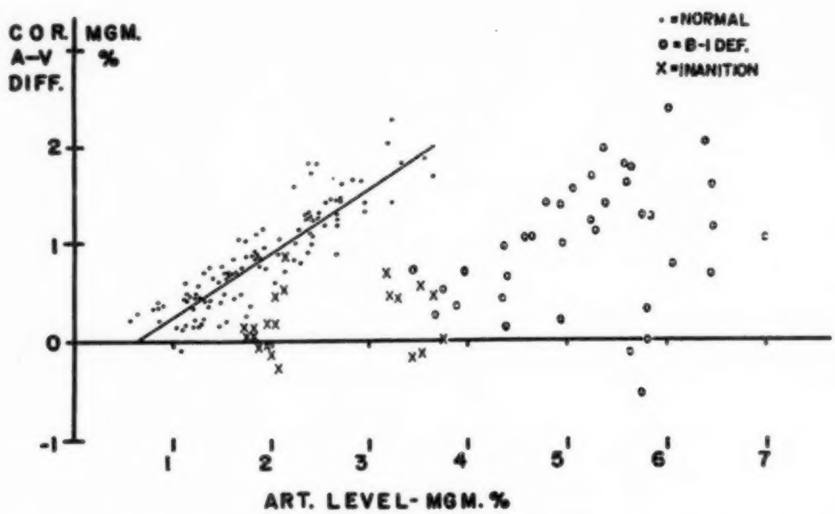

Fig. 2.—Relation of coronary arteriovenous differences to arterial levels of pyruvate.

Fig. 3.—Relation of oxygen extraction coefficient to coronary blood flow.

The mean coronary arteriovenous difference, coefficient of extraction, and total utilization of glucose are below normal in both the thiamin-deficient and starved dogs.

2. *Chronic Thiamin Deficiency.*—In chronic thiamin deficiency the arterial levels of lactate and pyruvate are higher but the arteriovenous differences are relatively lower than when the same dogs were in a normal state (Table III). Thus, the coefficient of extraction is decreased for each substance.

TABLE III. METABOLIC FINDINGS IN THREE ANESTHETIZED DOGS BEFORE AND DURING CHRONIC THIAMIN DEFICIENCY

DOG NO.	CONDITION	LACTATE			PYRUVATE		
		ART. (MG. %)	A-V (MG. %)	C. EXT. (%)	ART. (MG. %)	A-V (MG. %)	C. EXT. (%)
53	Normal	8.4	3.9	46.5	1.21	0.58	48.0
	Athiaminosis	13.5	2.9	21.5	2.02	0.45	22.2
57	Normal	8.8	2.8	31.8	0.68	0.29	42.6
	Athiaminosis	13.5	3.8	28.1	1.72	0.49	28.5
58	Normal	8.1	3.9	48.1	1.23	0.52	42.2
	Athiaminosis	12.0	2.0	16.7	1.53	0.35	22.8

Abbreviations. See Table I.

B. Oxygen Utilization

The total left ventricular utilization of oxygen in the thiamin-deficient animals is 14.0 c.c./100 Gm./1 which is significantly less than that for the normal animals (19.5 c.c./100 Gm./1). It is also less than the mean for the starved dogs of 20.9 c.c./100 Gm./1 (extremes from 18.4 to 24.3), but the data in the starvation group are insufficient for statistical evaluation. Figure 3 demonstrates the lack of correlation of the myocardial oxygen extraction coefficient (A-V/A) and the coronary flow in normal and starved dogs. The extraction of oxygen in these animals is not limited by the speed of the coronary flow but is apparently dependent on other factors. In the thiamin deficient dogs, however, Fig. 3 shows a striking limitation on the oxygen coefficient of extraction at higher levels of coronary flow.

C. Hemodynamic Findings

The detailed hemodynamic findings in the seven dogs with acute thiamin deficiency are given in Table I, and in Table II the mean values are compared with the normal and inanition controls.

D. Electrocardiographic Changes

Since Nembutalization alone results in various unpredictable electrocardiographic changes, the only reliable findings are in the six unanesthetized dogs. Deeply inverted T waves are found in all three limb leads as the thiamin deficiency develops. In addition, a marked sinus arrhythmia is present in five of the dogs, together with some bradycardia. The normal mean pulse rate of the unanesthetized dogs is 108 beats per minute, which decreases to a mean of 73 per minute during acute thiamin deficiency. It is interesting that following Nembutalization there is a tachycardia (average pulse of 179) in the thiamin-deficient dogs, and the sinus arrhythmia is abolished. A probable explanation is the known atropine-like effect of Nembutal.

DISCUSSION

The myocardial utilization of pyruvate and lactate was found to be abnormal in thiamin-deficient dogs. The data are consistent with the established role of thiamin-pyrophosphate in catalyzing the decarboxylation of pyruvate.

The normal relationship between arterial pyruvate and myocardial extraction of pyruvate is distributed in thiamin deficiency. The myocardial coefficient of extraction of pyruvate is significantly decreased, and its threshold of utilization markedly increased. The thiamin-deficient dog is able, however, to attain reasonably normal absolute extraction rates at the elevated arterial pyruvate levels which are present. This may be considered analogous to the metabolic findings in diabetes mellitus, wherein carbohydrate metabolism is limited by a relative deficiency of another physiologic catalyst, insulin. In this situation a normal level of glucose utilization is attainable only at elevated arterial glucose levels.[5] The present observations are consistent with studies by Olson and associates[6] who demonstrated decreased pyruvate utilization by thiamin-deficient rat and duck ventricle slices at the same initial level of pyruvate in vitro. The degree of the inhibition of pyruvate utilization was directly proportional to the thiamin content of the ventricle.

Despite the very high mean arterial lactate level, the mean coronary arteriovenous difference was decreased significantly below normal and the coefficient of extraction was therefore lower. The total lactate utilization in milligrams/100 grams of left ventricle/minute was also significantly lower than normal. The finding of a decreased coronary arteriovenous difference of lactate in thiamin deficiency is in accord with the work of Randles and associates.[7] Randles, however, did not include any starvation controls in his study. We have shown[2] that starvation causes as great a decrease in the lactate arteriovenous difference as does athiaminosis. Because the arterial lactate is higher in the thiamin-deficient group, however, it shows a significantly reduced coefficient of extraction of lactate. Previous in vivo[2] and in vitro[8] studies have demonstrated a direct relation between the availability of lactate and its rate of utilization in normal animals. Therefore, the high arterial lactate level in thiamin-deficient dogs in contrast to the low level in starved dogs, together with equally low arteriovenous differences,

would indicate a severe block in lactate utilization in athiaminosis. This is also indicated by the markedly increased threshold of utilization of lactate in the thiamin-deficient dogs.

Although the utilization thresholds and arterial levels of both pyruvate and lactate were markedly elevated during thiamin deficiency, lactate extraction was inhibited much more than pyruvate extraction. This apparently exaggerated defect in the utilization of lactate as compared with pyruvate could be due to the adverse effects of elevated pyruvate levels upon lactic dehydrogenase. The equilibrium constant for this enzyme actually favors lactate formation and this effect would be increased with high pyruvate levels. This has been shown by Brin and Olson[9] who observed that the utilization of lactate by duck ventricle slices was progressively depressed by increasing concentrations of pyruvate, but that pyruvate utilization was not inhibited by the presence of lactate.

In the dogs with chronic thiamin deficiency the decreased myocardial extraction coefficients for lactate and pyruvate offer additional evidence that the myocardial utilization of these substances is abnormal during thiamin deficiency. The factor of starvation can be excluded in these dogs since they were eating well and showed only a very slight weight loss.

The experiments herein reported confirm previous in vitro observations of decreased oxygen utilization by various tissues during thiamin deficiency. Peters and Thompson[10] showed a decreased oxygen utilization by pigeon brain which was increased by addition of thiamin. Sherman and Elvehjem[11] demonstrated decreased oxygen consumption by thiamin-deficient minced chick heart, and Muss and associates[12] found decreased auricular oxygen consumption, but normal ventricular oxygen consumption by thiamin-deficient rat heart slices. Olson and associates[5] found decreased oxygen consumption by thiamin-deficient heart ventricle slices with added pyruvate in ducks but not in rats. In the present studies the thiamin-deficient dogs showed an abnormal relationship of their myocardial oxygen extraction coefficient to the rate of the coronary flow. In normal and starved animals the extraction coefficient bore no relation to coronary flow, whereas the extraction coefficient in thiamin-deficient dogs was markedly limited at higher levels of coronary flow. This defect in oxygen extraction may be interpreted as indicating a metabolic block that limits the speed of oxygen extraction. In addition to this, the total left ventricular oxygen consumption was significantly decreased in the thiamin-deficient dogs. This was probably related, however, to the significantly lower level of left ventricular work in the vitamin-deficient dogs, so that the left ventricular efficiency was approximately the same in all three groups of animals.

SUMMARY AND CONCLUSIONS

1. An abnormal pattern of myocardial metabolism has been demonstrated in dogs during acute and chronic thiamin deficiency.

2. In the face of markedly elevated arterial pyruvate in acute thiamin deficiency, the coronary arteriovenous difference and total utilization of pyruvate

were maintained within normal limits. The threshold of utilization of pyruvate was significantly increased, however, and the coefficient of extraction was decreased.

3. Lactate extraction was apparently inhibited more than pyruvate, possibly due to the adverse effects of elevated pyruvate levels on lactic dehydrogenase.

4. Glucose extraction by the myocardium was also below normal in acute thiamin deficiency but was not different from the findings in starved dogs.

5. An abnormality in oxygen utilization was demonstrated by the limitation placed on the myocardial oxygen extraction coefficient by higher rates of coronary flow in acute thiamin deficiency.

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PRIMARY CARDIAC AMYLOIDOSIS

ALEXANDER I. THOMASHOW, M.D., WILLIAM D. ANGLE, M.D., AND
THOMAS G. MORRIONE, M.D.

NEW YORK, N. Y.

PRIMARY or atypical amyloidosis has been receiving increasing attention in recent years. In 1935, Reimann and associates[1] proposed the following classification of amyloidosis: (1) secondary amyloidosis; (2) primary amyloidosis; (3) amyloidosis associated with multiple myeloma; and (4) tumor-forming amyloidosis. Secondary amyloidosis was so designated because of its invariable association with pre-existing disease, such as tuberculosis or chronic suppuration. In this type the deposits of amyloid are most marked in the liver, spleen, kidneys, and adrenals although it may occur in other sites including the heart. Primary or atypical amyloidosis was so named because of its occurrence in the absence of predisposing disease states and because of its "atypical" amyloid distribution. Usually it involves sparingly the abdominal parenchymatous organs whereas heavy depositions in the heart, tongue, gastrointestinal tract, lungs, smooth and skeletal musculature, skin and lymph nodes are characteristic. Multiple myeloma is accompanied by an amyloid deposition resembling the primary variety in from 6 to 10 per cent of all cases. Tumor-forming amyloidosis is the least common type and occurs as localized tumefactions in the skin and various mucous membranes where it may simulate neoplastic infiltration.

Koletsky and Stecher[2] in 1939 reviewed twenty-two cases of primary amyloidosis and reported one of their own. The ages of their patients varied from 36 to 72 years and averaged 52 years. All of these cases showed multiple organ involvement, and the heart was involved in nineteen of the cases. In 1946, Lindsay[3] reviewed an additional twenty-one cases and reported one of his own. He observed that twenty-three of the forty-five cases described in the literature had shown evidence of congestive failure and eighteen of these were considered to have died from congestive failure. Of the forty-three cases which had been autopsied, thirty-nine had cardiac involvement. He pointed out that signs and symptoms suggesting cardiac disease may be produced in primary systemic amyloidosis by involvement of the lungs, trachea, and mediastinum, or by an associated anemia. He further observed that congestive heart failure in these cases may result from pulmonary involvement with cor pulmonale, cardiac blood

From the Departments of Medicine and Pathology of the Long Island College Hospital and the Departments of Medicine and Pathology of the State University of New York College of Medicine New York, N. Y.

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vessel involvement, interstitial myocardial infiltration with or without secondary myocardial degeneration, pericardial or endocardial involvement, valvular deposition, or involvement of a combination of sites. Speaking on the classification of amyloidosis, he concluded, ". . . that when the basic mechanism is known, primary amyloidosis will be classified as a 'secondary' type."

In 1948, King[4] reported six cases of atypical amyloidosis. Five of these cases were unusual in that the patients were of advanced age and the amyloid was present almost exclusively in the heart. The ages of the five cases varied from 83 to 93. In two cases the amyloid was limited to the heart, in two other cases amyloid was also present in the pulmonary alveolar walls, and in the other case amyloid was also found in pulmonary vessels. He proposed that these cases be classified as ". . . atypical amyloidosis associated with senility." Considering all types of amyloidosis he suggested the following new classification: (1) typical amyloidosis: deposition of amyloid in the usual sites (kidneys, spleen, liver, adrenal, etc.), (a) associated with other disease (as tuberculosis, multiple myeloma, carcinoma, osteomyelitis), (b) not associated with other disease (rare, but occasionally reported as "primary"); (2) atypical amyloidosis: amyloid not following the usual or typical distribution, found in one or many foci or organs with or without symptoms, (a) associated with other disease or condition (as multiple myeloma, Hodgkin's disease, carcinoma, pyelonephritis, bronchiectasis, and the like), (b) not associated with other disease (including most of the cases reported in the literature as primary amyloidosis, whether systemic or local).

Higgins and Higgins[5] in 1950 reported a case of primary systemic amyloidosis and reviewed the clinical manifestations of seventy cases described in the literature. They found the following manifestations at the indicated frequencies: congestive heart failure, 56 per cent; general muscular weakness, 50 per cent; weight loss, 40 per cent; macroglossia, 40 per cent; amyloid deposits in the skin and buccal mucosa, 33 per cent; dysarthria with macroglossia, 29 per cent; lymphadenopathy, 27 per cent; pain in the extremities, 24 per cent; dysphagia with macroglossia, 23 per cent; hypertension (blood pressure above 140/90 mm. Hg), 20 per cent; purpura, 15 per cent; abdominal pain, 12 per cent; pruritis, 7 per cent; hematuria, 7 per cent; epistaxis, 5 per cent; elevated temperature, 5 per cent; hematemesis, 4 per cent; and a history of allergy, 3 per cent.

In 1950, Jones and Frazier[6] described fifteen cases of "cardiovascular amyloidosis." The amyloid deposition was limited to the heart in five cases, and in one case amyloid was present in the heart and in the epicardial fat. In the other nine cases amyloid was present in the heart and in pulmonary vessels, periadrenal vessels, alveolar walls, epicardial fat, or other sites. The ages of their patients varied from 55 to 101 years and the average age was 72 years. In 1952, Josselson and associates[7] reported a series of twenty-nine cases of "amyloid localized to the heart." In eighteen of these cases the amyloid was limited to the heart while in the remaining eleven cases minute amounts were found in the pulmonary alveolar septa, pulmonary vessels, periadrenal blood vessels or small pancreatic and renal blood vessels. The ages of their patients varied from 63 to 100 years and the average age was 82 years. Congestive failure was present in six cases.

Carcinoma was found in twelve cases and multiple myeloma in one case. Since Higgins and Higgins reviewed the literature in 1950 several additional case reports of primary systemic amyloidosis involving the heart have been described in the literature.

Two cases of amyloidosis limited to the heart and one case of amyloidosis involving the heart and pulmonary vessels and alveolar walls are reported.

CASE REPORTS

CASE 1.—An 85-year-old man was admitted on April 18, 1952 to the Urologic Service complaining of inability to void for the preceding 24 hours. During the month previous to admission the patient had noted increasing difficulty in urination. Three days prior to admission he suffered the onset of chills and fever which persisted. There was a past history of an alleged myocardial infarction two years preceding admission. The patient had experienced exertional dyspnea, ankle edema, and left-sided chest pain for an undeterminable period.

Physical examination: Temperature, 103° F; pulse, 112; respirations, 42; blood pressure, 210/94 mm. Hg. The patient was orthopneic and slightly cyanotic. The right lung was hyperresonant to percussion and basilar râles were present. The left lung was clear from the apex to the fourth rib posteriorly with dullness and absence of breath sounds below this level. The heart was enlarged to both the right and left. There was a grossly irregular rhythm at a rate of 112 beats per minute. The heart sounds were of poor quality and a soft systolic murmur was heard at the apex. There were tenderness and a sense of fullness in the epigastrium. A large right inguinal hernia was present. The prostate was moderately enlarged and firm.

Laboratory data: Red blood count, 4.44 million; hemoglobin, 11.5 grams; white blood count, 20,950, with 75 neutrophiles, 20 lymphocytes, and 5 monocytes. The serology was negative. The blood chemistries were: sugar 113 mg., urea 49.2 mg., and creatinine 1.7 mg. per cent. The urine was acid with a specific gravity of 1.024, 3-plus albumin, and otherwise negative.

Course: The patient was placed on bed rest, salt-free diet, and aqueous penicillin 100,000 units every three hours. Indwelling catheter drainage was instituted. He was digitalized and given an injection of a mercurial diuretic. By the third hospital day the patient exhibited only a low grade temperature, the heart rate was 90 and irregular, and the dyspnea lessened. The following day an electrocardiogram showed auricular fibrillation and left bundle branch block. A chest roentgenogram demonstrated a marked bronchopulmonary reaction in the right middle lung field, extensive pleural effusion on the left, and marked elongation and dilatation of the aorta with an aneurysmal dilatation in the region of the arch. Some flecks of calcium were noted in the descending portion of the aorta but none in the aneurysmal portion.

On the seventh hospital day a gastrointestinal series was performed and was negative other than that the upper portion of the esophagus was displaced posteriorly by the aortic aneurysm. At noon on the eighth day the patient expired suddenly.

Autopsy findings: The patient weighed approximately 175 pounds. Externally, cyanosis of the skin of the head and neck was present. The left pleural space contained approximately 800 c.c. of degenerating reddish-brown blood. The heart weighed 550 grams. There was slight dilatation of the left atrium. The mitral valve measured 10 cm. in circumference and the leaflets were grossly not remarkable. The left ventricle measured 2 cm. in thickness and the chamber appeared moderately dilated. Mild atheromatous thickening of the intima of the coronary arteries and slight tortuosity of the vessels were apparent. The myocardium grossly was firm, beefy red and on serial section presented no abnormalities. The aorta showed a sacular aneurysm in its arch. The aneurysm measured 7 cm. in diameter and was almost completely filled by fibrous tissue. It communicated with the lumen of the aorta through an opening 4 cm. in diameter situated 4 cm. above the aortic valve. There was a rupture in the wall of the aneurysm through which blood escaped into the left pleural space. Severe atheromatosis of the aorta was apparent especially in its abdominal portion. Both lungs on section showed considerable oozing of frothy pinkish fluid from their cut surfaces. The spleen weighed 100 grams and was grossly normal.

The liver weighed 1,280 grams and showed a normal architecture and gross appearance. No abnormalities of the pancreas or adrenals were noted. The kidneys were of approximately equal and normal size and showed slight surface cortical granularity after the capsules had been stripped. No gross abnormalities of the prostate, testis, thyroid and gastrointestinal tract were noted.

Microscopic description: Heart: Sections of the left ventricle showed hypertrophy of myocardial fibers. Scattered throughout the myocardium there were occasional small interstitial collections of pale hyaline acidophilic material. This frequently surrounded individual myocardial fibers which were atrophic in these regions. Collections of amyloid were also seen in the wall of the right ventricle, but here it was considerably less in amount and limited almost exclusively to the columnae carneae. In addition to the amyloid, there were a few scattered minute foci of myocardial interstitial fibrosis. Special stains showed the cardiac amyloid to give a positive staining reaction with crystal violet and Congo red, and a negative reaction with iodine staining. The wall of the aortic aneurysm was thin and comprised almost exclusively of dense hyalinized fibrous tissue. In this as well as in the adventitia there were focal collections of lymphocytes. There was a large adherent intimal thrombus which showed minimal organization. Microscopically, as an incidental finding, an adenocarcinoma of the prostate gland was observed.

Anatomic diagnosis: Aneurysm of arch of aorta; thrombosis of aortic sacular aneurysm; atherosclerosis of aorta; atelectasis of left lung; edema of lungs; left hemothorax with fibrinous pleurisy; adenocarcinoma of prostate gland; fatty infiltration of pancreas; primary cardiac amyloidosis.

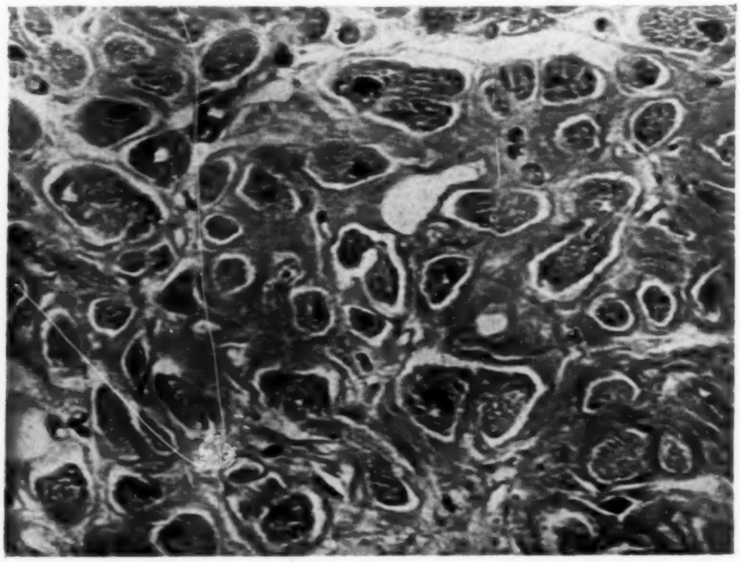

Fig. 1.—Case 1. Section of left ventricle showing large amounts of amyloid between myocardial fibers. The amyloid completely encircles many of them and some of the fibers are atrophic. No inflammatory reaction is present. (Magnification ×400. Hematoxylin and eosin stain.)

CASE 2.—An 89-year-old white man was admitted to the Medical Service on Jan. 20, 1951 in coma. The patient had apparently enjoyed good health until 2 months preceding admission at which time he either fell while getting out of bed or lost consciousness and fell out of bed. Subsequently his lower extremities were paretic, he underwent a personality change, and he experienced difficulty in swallowing and occasional episodes of dyspnea. Shortly before entry the patient developed urinary and fecal incontinence. On the afternoon of admission the patient had a convulsive seizure and lapsed into coma.

Physical examination: Temperature, 101° F.; pulse, 102; respirations, 16; blood pressure, 192/100 mm. Hg. The patient was in good nutritional state. There were bilateral cataracts.

There was slight cyanosis of the lips. There were a few rhonchi scattered throughout the chest. The heart was slightly enlarged with the point of maximum intensity at the mid-clavicular line in the fifth intercostal space. The rhythm was grossly irregular. There was an apical systolic murmur. The second pulmonic sound was accentuated. The abdomen was distended and tympanitic, and the urinary bladder was markedly distended. The patient moved his upper extremities spontaneously and the lower extremities in response to painful stimuli. The abdominal reflexes were absent, the knee jerks were active and equal, and no response was obtained on plantar stimulation.

Laboratory data: Red blood count, 4.65 million; hemoglobin, 14.1 grams; white blood count, 10,550, with 76 neutrophiles, 18 lymphocytes, and 6 monocytes. The sedimentation rate was 48 mm. per hour. The serology was negative. The blood chemistries were: sugar 146 mg., urea 55.2 mg., creatinine 1.9 mg., and chlorides 586 mg. per cent; carbon dioxide content 76.2 volumes per cent. Urinalysis revealed a reddish urine with a pH of 4.5, specific gravity 1.017, 2-plus albumin, and moderate numbers of white blood cells and many red blood cells in the sediment.

Course: The patient was given oxygen and parenteral fluids. A spinal tap revealed normal fluid pressure and dynamics. The cell count, serology, and protein were normal. An electrocardiogram showed auricular fibrillation at a rate of 80 with depression of the RS-T segment in Leads II, III, V_4 and V_6. The interpretation was left ventricular strain and digitalis effect. Continuous catheter drainage was instituted. The patient regained consciousness on the second hospital day and was restless and complaining of abdominal pain. The abdomen remained distended, and the patient had low grade temperature.

On the fourth hospital day the temperature spiked to 104.4° F. and the patient lapsed again into coma. The catheter drainage became bloody. The heart rate rose to 120 and moist râles appeared at both bases. The patient was given 1.2 mg. of digitoxin and was placed on procaine penicillin 300,000 units every 12 hours and dihydrostreptomycin 0.5 Gm. every six hours. During the subsequent course the patient was in varying depths of stupor. A moderate temperature continued. The blood pressure varied from 90/50 to 180/80 mm. Hg. The abdomen continued distended despite several successful Harris drips. A roentgenogram of the abdomen demonstrated marked gaseous distention of both the large and small bowel. On the eleventh day the temperature increased and the heart rate rose to 120. The condition deteriorated, and the patient died on the fifteenth day.

Autopsy findings: The body was that of an elderly white, extremely obese man weighing approximately 180 pounds. Bilateral cataracts were present. Both pleural cavities were partially obliterated by moderately firm, glistening, fibrous adhesions. The pericardial sac contained approximately 50 c.c. of clear straw-colored fluid. The heart weighed 440 grams and showed left ventricular enlargement on inspection. The atria were of the usual size. The endocardium of the left atrium showed a well-circumscribed elevated plaque measuring 1.5 cm. in diameter near the base of the posterior mitral leaflet. Its surface was roughened and covered by a small amount of dull tan friable thrombus. The remaining endocardium of atria and ventricles was smooth, semitranslucent, glistening and trabeculated. The cardiac valves all showed relatively thin, semitranslucent leaflets. The left ventricular wall and papillary muscles and columnae carneae appeared markedly thickened. The myocardium on section was uniformly finely granular, glistening and tan in color. The coronary arteries were markedly calcified and their lumina partially obliterated by intimal thickening. The aorta showed numerous atherosclerotic intimal plaques throughout its entire course. Many of these were ulcerated and calcified.

The right lung weighed 530 grams and the left lung 420 grams. The bronchi contained a moderate amount of thick brownish mucoid material. The pulmonary arteries showed scattered, slightly raised intimal yellowish plaques. The lung parenchyma appeared diffusely dull and dark red and was somewhat firmer than usual. On section the lobes showed a rather dull, pink tan and finely granular appearance. Emphysematous blebs were present in both upper lobes, and the cut surfaces exuded only a slight amount of pinkish fluid. The spleen weighed 100 grams. It showed no gross abnormalities. No changes of note were apparent grossly in the gastrointestinal tract, liver, gall bladder, pancreas, or adrenals. The kidneys were of approximately equal and average size and showed cortical cysts varying from 1.5 to 3 cm. in diameter. The capsules stripped with difficulty revealing roughly granular, glistening, purplish-tan external surfaces showing tiny, stellate, compressed scattered regions. The brain showed no unusual findings.

Microscopic description: Heart: Throughout all sections of both ventricles and atria as well as the left auricular appendage there were large deposits of amyloid. This was distributed in a focal confluent and diffuse pattern. The amyloid occurred between muscle fibers and frequently replaced them completely throughout large zones. In other areas it encircled atrophic persisting myocardial fibers. The amyloid was virtually acellular, acidophilic, hyaline and rarely traversed by a partially collapsed capillary. The valve leaflets themselves showed no infiltration by amyloid but in the wall of the left atrium there were small amounts of amyloid deposited beneath the thickened endocardium. The left auricular appendage contained amyloid within its wall and it showed an adherent partially calcified and poorly organized healed thrombus. There was slight hypertrophy of myocardial fibers especially in the wall of the left ventricle and here too a rare interstitial focus of fibrosis was seen. Special stains showed the cardiac amyloid to be crystal violet and Congo red positive, and iodine negative.

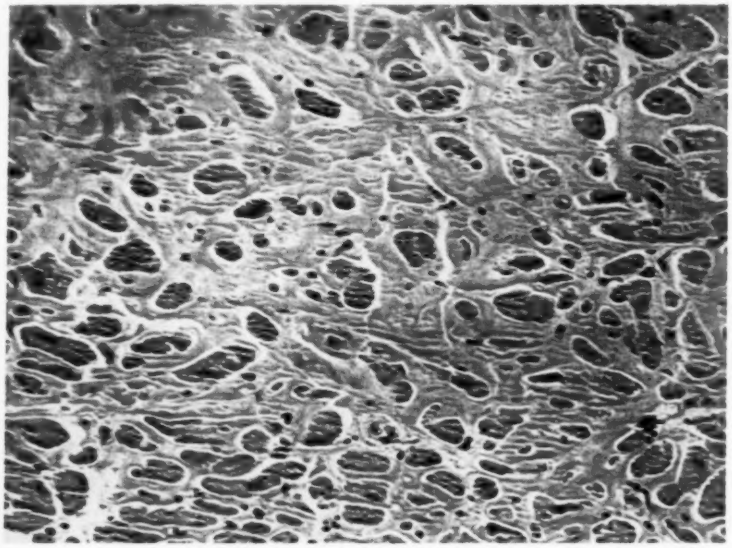

Fig. 2.—Case 2. Section of left ventricle showing extensive interstitial collections of amyloid between myocardial fibers. Some fibers are atrophic. The tissue is poorly vascularized and shows no inflammatory reaction. (Magnification ×200. Hematoxylin and eosin stain.)

Lungs: Throughout all sections there were deposits of palely basophilic or acidophilic amyloid within alveolar walls. This change sometimes increased the thickness of the alveolar septa three or four times their average caliber and at the free ends of the septal walls produced rounded, hyaline structures which were avascular and covered by surface endothelium. Smaller amounts of amyloid were encountered in the walls of small arteries, primarily in their subintimal layers. No amyloid was present in the walls of the bronchioles. Elsewhere, the lung showed patchy atelectasis, hemorrhage, and congestion. Numerous, rounded, amylaceous bodies were present within alveolar spaces. Special stains showed staining reactions identical with those observed in the cardiac amyloid.

In the spleen there were scattered regions of recent hemorrhagic infarction. No amyloid infiltration was present. The liver was free of amyloid. The adrenals and pancreas showed nothing of note. In the kidneys there were numerous scattered cortical foci of interstitial and glomerular fibrosis, lymphocytic infiltration, and tubular atrophy. No amyloid was present.

Anatomic diagnosis: Primary amyloidosis of heart and lungs; thrombosis of left auricular appendage; hypertrophy of heart; recent infarcts of spleen; nephrosclerosis; acute colitis; atrophy of testis with Leydig's cell hyperplasia; healed tuberculosis of lungs and hilar lymph nodes.

CASE 3.—A 74-year-old white man was first admitted to the Medical Service on June 22, 1946 for shortness of breath and temperature. Approximately 25 years preceding admission the patient commenced to suffer a chronic productive cough during the winter months. A few years prior to admission these episodes began to be accompanied by wheezing respiration and shortness of breath, which were frequently of sufficient severity to restrict the patient to bed. There was no history of chest pain or hemoptysis. One week previous to entry the patient developed the symptoms of an upper respiratory infection which were followed by wheezing respirations, shortness of breath, general malaise, and fever. Two days prior to admission the dyspnea became worse and ankle edema was noted for the first time. On the day before entry the patient was seen by a physician and was given 1.2 mg. of digitoxin and was placed on sulfadiazine.

The past history disclosed the presence of psoriasis for 7 years, right-sided inguinal hernia for 5 years, and an anal fistula for 10 years.

Physical examination: Temperature, 101.8° F.; pulse, 84; respirations, 34; blood pressure, 124/62 mm. Hg. The patient was moderately obese. Psoriatic lesions were scattered over the body including the scalp. Slight cyanosis was present. There was bilateral conjunctivitis. The nose and throat were diffusely injected. A number of moderately sized lymph nodes were palpated in the neck. The chest was symmetrical with an increase in the anteroposterior diameter. There were dullness, diminished breath sounds, increased fremitus, and coarse moist râles at both bases especially the right. Cardiac percussion was unsatisfactory and the apex impulse was not palpable. The heart sounds were of moderate intensity. There was a systolic murmur loudest at the apex and audible along the left sternal border. The second pulmonic sound was accentuated. The abdomen was distended. There was mild pitting edema of the ankles.

Laboratory data: Hemoglobin, 13.5 grams; white blood count, 12,200, with 80 neutrophiles, 12 lymphocytes, and 8 monocytes. The sedimentation rate was 46 mm. per hour and the hematocrit 40 mm. The blood chemistries were: sugar 106 mg., urea 35.7 mg., creatinine 1.3 mg., cholesterol 247 mg., and bilirubin 0.37 mg. per cent. The serum albumin and globulin were 3.7 and 3.9, and 2.8 and 2.3 grams per cent, respectively, on two occasions. The cephalin flocculation was 1-plus and negative on two occasions. Five urinalyses were negative for albumin, sugar, or significant sediment and had specific gravities ranging up to 1.017. A throat culture showed hemolytic streptococcus predominating.

Course: The patient was placed on bed rest, continuous oxygen, sedation, 0.2 mg. digitoxin daily, and aqueous penicillin 50,000 units every 3 hours. A chest roentgenogram disclosed pneumonitis in the right lower lung field, elongation and arteriosclerosis of the aorta, and cardiac enlargement, left ventricular in type. The venous pressure was 210 mm. of water. A phlebotomy of 560 c.c. was performed. The patient responded well to therapy. The heart rate was controlled and the temperature soon became low grade and fell to normal in ten days. Venous pressure determinations on the third and eleventh hospital days were 190 and 160 mm., respectively. The chest signs cleared except for dry râles which were controlled with parenteral aminophylline. The patient resumed activity and was discharged after two weeks' hospitalization.

The patient was readmitted on June 25, 1951, complaining of increasing cough, shortness of breath, and ankle edema. In the interval following discharge he had been maintained on digitoxin, salt restriction, limited activity, aminophylline, and periodic mercurial injections.

Physical examination: Temperature, 100° F.; pulse, 90; respirations, 32; blood pressure, 120/70 mm. Hg. Psoriatic lesions were present as before. There was slight cyanosis and moderate conjunctival injection. The chest was emphysematous in contour and moist râles were heard at both bases. The heart was enlarged to the left to percussion and the heart sounds were of fair quality. The liver edge extended four finger breadths below the costal margin and was tender. There was minimal ankle edema.

Laboratory data: Red blood count, 5.53 million; hemoglobin, 16 grams; white blood count, 7,600, with 73 neutrophiles, 23 lymphocytes, 2 monocytes and 2 basophiles. The sedimentation rate was 5 mm. per hour and the hematocrit 54. The blood serology was negative. The blood chemistries were: sugar 100 mg., urea 42.8 mg., creatinine 1.6 mg., cholesterol 308 mg., cholesterol esters 132 mg., sodium 332 mg., potassium 22.2 mg., and chlorides 498 mg. per cent, and carbon dioxide content 95, 95.4, and 81 volumes per cent on three occasions. The urinalysis was negative.

Course: The patient was placed on bed rest, low-sodium diet, oxygen, digitoxin 0.1 mg. daily, aminophylline, potassium iodide, and mercurial injections. Temperature, which responded to penicillin, was present for a few days. A chest roentgenogram showed cardiac enlargement, elongation, and dilatation of the aorta, and some areas of infiltration and atelectasis in the right lower lobe in the region of the previous pneumonia. An electrocardiogram showed right axis deviation with depression of the S-T segment in Leads I, II, III, aV_F, and V_2, V_4, and V_6. There was a deep S wave in Leads I and aV_L and in all the precordial leads. There was a tendency to low voltage in the limb leads with the largest QRS amplitude being 6.5 mm. in Lead II. The P-R interval was 0.08 second. The interpretation was nodal rhythm, right ventricular strain, digitalis effect, and tendency to low voltage. An electrocardiogram ten days later showed auricular fibrillation with multifocal premature ventricular beats but was otherwise similar. The venous pressure was 155 mm. of water, the Decholin circulation time 11 seconds, and the ether circulation time 6.5 seconds. The patient was discharged considerably improved on the thirteenth hospital day.

The patient was readmitted for the last time on July 8, 1951, 32 hours following discharge. Shortly before admission, while using a bedpan at home, the patient suddenly became flushed and cyanotic and lapsed into unconsciousness. He was brought to the hospital admitting room where he was found to be pulseless. Consciousness had returned, and the patient was very restless. Aminophylline, sedation and oxygen were administered as emergency measures with considerable improvement.

Physical examination: Temperature, 97.8° F.; pulse, 48; respirations, 24; blood pressure, 110/30 mm. Hg. There was moderate cyanosis. The neck veins were distended. Moist râles filled the lower half of both lung fields. The heart sounds were weak, and auricular fibrillation was present. The liver edge extended four finger breaths below the costal margin and was tender. There was minimal peripheral edema.

Course: An electrocardiogram taken shortly after admission disclosed auricular fibrillation with a high degree of auriculoventricular block and multifocal ventricular beats at a slow rate. The patient was placed on oxygen and ephedrine sulfate 45 mg. every four hours, but the slow ventricular rate continued and the patient died sixteen hours after admission.

Autopsy findings: The body was that of an elderly white man weighing approximately 135 pounds. Deep cyanosis of the nail beds was prominent. The heart weighed 490 grams, largely because of left ventricular enlargement. The valve leaflets showed thickening of their margins and bases but no changes of note in the commissures or chordae tendineae. The right auricular appendage was dilated and contained a loosely adherent mural thrombus measuring 3 to 4 cm. in average dimension. The left ventricular wall showed a thickened firm, dark red myocardium. The coronary arteries showed scattered shallow gray and yellowish atheromatous plaques which did not significantly encroach upon the vessel lumina. The left ventricular wall measured 2.5 cm. in thickness. The right lung weighed 320 grams and the left lung 280 grams. Both lungs had a soft and feathery consistency and pitted very easily and deeply with gentle pressure. Scattered emphysematous blebs were present along some of the borders of the lower lobes. The spleen weighed 120 grams and on section had a hard consistency and showed sharp edges. The liver weighed 950 grams and on section showed a nutmeg appearance. No gross abnormalities were present in the gall bladder, pancreas, and adrenals except for a solitary calculus within the gall bladder lumen which was rounded and measured 6 mm. in diameter. The right and left kidneys weighed 110 and 130 grams, respectively, and showed a finely granular external surface. The mucosa of the stomach and of the small and large intestines showed diffuse congestion and scattered areas of hemorrhagic change with no discrete ulceration. The stomach and entire intestinal tract contained fluid and partially clotted blood.

Microscopic description: Throughout all sections of both ventricles and atria, there were intramural deposits of hyaline acidophilic amyloid. This had a patchy focal distribution and in some regions completely replaced myocardial fibers. The endocardium of the left atrium was thickened and showed focal subendocardial deposits of amyloid. The columnae carneae contained large deposits of amyloid but the mitral valve showed none. The right auricular appendage con-

tained a partially organized thrombus and in its wall there were numerous focal deposits of amyloid. There was hypertrophy of myocardial fibers especially in the wall of the left ventricle. A section of the left coronary artery showed marked intimal fibrous thickening. The mucosa of the stomach and of the small and large intestines showed marked congestion of capillaries and foci of stromal hemorrhage. These for the most part were recent but in scattered regions there were hemosiderin-laden macrophages. In one area the colon showed extensive mucosal hemorrhage and focal ulceration. The hemorrhage, here too, extended into the edematous submucosa, and the latter was infiltrated by numerous neutrophiles. Hyalinization of a few islands of Langerhans was noted in the pancreas. Special stains revealed negative staining for amyloid in the islet tissue with crystal violet, Congo red and iodine. The myocardial amyloid also gave a negative staining reaction with crystal violet and iodine but took a deep reddish orange stain with Congo red.

Anatomic diagnosis: Primary cardiac amyloidosis; hypertrophy of heart; thrombosis of right auricular appendage; chronic passive congestion of liver, spleen and kidneys; emphysema of lungs; nephrosclerosis; acute hemorrhagic gastritis, enteritis, and colitis; cholelithiasis; hyalinization of islands of Langerhans.

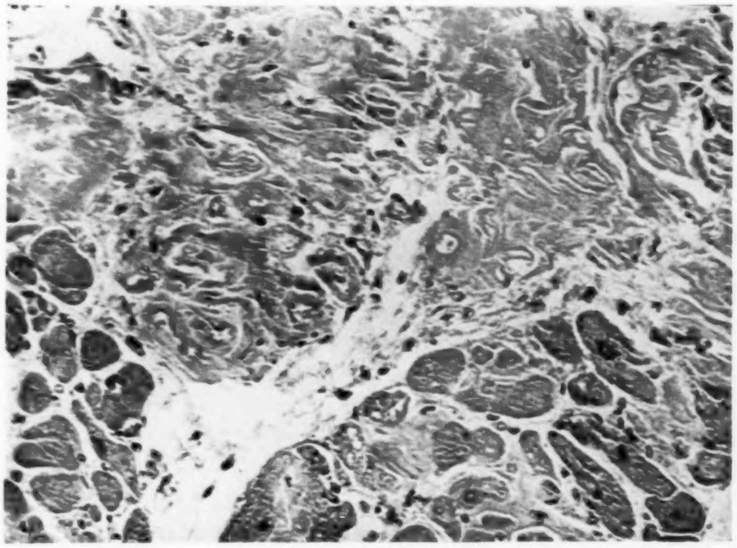

Fig. 3.—Case 3. Section of left ventricle near the epicardium. Large focus of amyloid deposition which in a portion of the field completely replaces myocardial fibers. The amyloid presents an irregularly hyalinized appearance. (Magnification ×200. Hematoxylin and eosin stain.)

DISCUSSION

Descriptions of cases showing amyloid localized to the myocardium raise the question as to whether these cases should be classified under a separate category. In reporting similar cases King proposed the classification "atypical amyloidosis associated with senility," Jones and Frazier used the term "cardiovascular amyloidosis," and Josselson, Pruitt, and Edwards used the phrase "amyloid localized to the heart." Factors which tend to favor the formation of a separate category are: (1) primary cardiac amyloidosis occurs in an older age group than systemic primary amyloidosis, (2) although extensive myocardial infiltrations with amyloid are seen in systemic primary amyloidosis, there is also considerable amyloid deposition in other sites. This distribution differs from that in primary

cardiac amyloidosis where extracardiac amyloid is either totally absent or present in insignificant amounts in alveolar walls, small vessels, or other sites. (3) In view of the present confused status of amyloidosis in general, establishing a separate category of primary cardiac amyloidosis may prove to be useful in facilitating future investigation of this disease.

The first patient had marked systolic hypertension and an aortic aneurysm. He was in congestive failure. The electrocardiogram showed auricular fibrillation and left bundle branch block. At autopsy the aneurysm was found to have ruptured, which was the presumed immediate cause of the death. Amyloid was found in small amounts in the heart. The second patient had a moderate systolic hypertension. The electrocardiogram demonstrated auricular fibrillation and left ventricular strain. The patient was in cardiac decompensation during the terminal illness. Post-mortem examination disclosed extensive amyloid deposition in the heart, and amyloid was also present in the alveolar walls and pulmonary vessels. The third patient had pulmonary emphysema and had been in varying degrees of congestive failure during the five years preceding death. The original electrocardiogram demonstrated nodal rhythm and right ventricular strain, while subsequent tracings showed a slow heart rate with auricular fibrillation and a high degree of atrioventricular block with multifocal ectopic ventricular beats. The later severe arrhythmia was the apparent cause of death. Post-mortem examination disclosed large amounts of amyloid throughout the myocardium.

With the increasing incidence of post-mortem discovery of cardiac amyloidosis, emphasis has been placed on modes of establishing the diagnosis clinically. It has been stated in the literature that persistent, nonresponsive congestive failure in an aged individual, in the absence of hypertension, valvular or coronary arterial disease, or other conditions generally associated with cardiac decompensation should lead one to suspect the presence of cardiac amyloidosis. However, congestive failure occurs in only about one-half of all cases and is resistant to therapy in only the more severe of these. Also, concomitant hypertension occurs in about 20 per cent of the cases and arteriosclerosis occurs with about the normal frequency. Furthermore, valvular lesions have been reported as a result of amyloid infiltration. Consequently, clinically one is reduced to the position of only being able to suspect the diagnosis in a small portion of cases.

Efforts directed at establishing a characteristic electrocardiographic pattern have also been disappointing. The reports of Wessler and Freedberg,[8] and Josselson and Pruitt[9] indicate that there are no characteristic findings. T-wave changes, auricular fibrillation, low voltage QRS, conduction defects, and various bizarre changes are frequently encountered. The frequency of auricular fibrillation has been stressed and may be attributable to the heavy auricular infiltration which is commonly noted.

The only laboratory procedure of any diagnostic value in primary amyloidosis is the Congo red test, but this has been positive in less than one-half of the few cases in which it was performed. The low incidence of positive tests has been attributed to the variable tinctorial properties of the amyloid and more especially to the relatively small amount of amyloid which may be present in cardiac amyloidosis. The serum globulin has been elevated in less than 10 per cent of the cases in which it has been determined. There are no characteristic hematologic findings.

In those cases of systemic primary amyloidosis where there is involvement of the skin, tongue, or other superficial tissue a biopsy will reveal the diagnosis, and this is the method by which most of the reported ante-mortem diagnoses were established. In most of these cases a gross abnormality was present, and the biopsy was undertaken to elucidate the nature of the lesion. Selikoff and Robizek[10] performed gingival biopsies on cases known to have secondary amyloidosis associated with tuberculosis, and they found a high incidence of positive biopsies despite the normal appearance of the gums. There are no reports of gingival biopsy for primary systemic amyloidosis, nor is it known if amyloid commonly occurs in the gingivae in primary systemic amyloidosis.

There is no known treatment for primary amyloidosis, and the disease is uniformly fatal. Remissions and cures of secondary amyloidosis have been reported following successful treatment of the underlying infection. Remissions and even cures have also been reported following therapy with prolonged high dosage of powdered liver extract orally.[11] There are no reports in the literature on the use of this therapy in primary amyloidosis. There is thus no known means at present of dealing with the amyloid per se, and treatment must consist of the usual measures employed in dealing with heart failure.

SUMMARY

Two cases of amyloidosis limited to the heart and one case of amyloidosis involving the heart and lungs are reported. All three patients were men in, or close to, the ninth decade of life. In all three cases auricular fibrillation and congestive failure were present. The literature is reviewed and a distinction drawn between systemic primary amyloidosis involving the heart and amyloidosis occurring in an advanced age group and involving the heart exclusively or almost exclusively. The term primary cardiac amyloidosis is proposed for the latter category. The difficulty of establishing a diagnosis of primary cardiac amyloidosis is discussed.

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TRANSMISSION OF ELECTROCARDIOGRAPHIC SIGNALS OVER TELEPHONE CIRCUITS

E. Grey Dimond, M.D., and Fred M. Berry

Kansas City, Kan.

In many rural areas there is a lack of professional personnel trained in accurate interpretation of the electrocardiogram. The use of suitable apparatus would make it possible for a physician to transmit the electrocardiogram via a standard telephone line to a medical center at any distance where it could be analyzed by experienced personnel. Such equipment would be of immense value to the military services. Small station hospitals, widely scattered, could immediately have the benefit of consultation from the thoroughly staffed general hospital.

We have developed such equipment and have found it simple and practical to operate.[1] Equipment for a similar purpose has been developed independently and concurrently by Rahm and associates.[2]

Figure 1 illustrates the transmitting equipment. This unit is compact and lightweight. A standard electrocardiograph machine (direct-writing or string) can be plugged into the unit at the left. Another connection leads to the telephone. Standard telephone equipment is used.

Figure 2 illustrates the receiver. We have modified a standard direct-writing machine, building the necessary receiving circuit into the single cabinet. If desired, a separate receiver can be made and simply attached to the side of the electrocardiograph.

At the transmitting end of the circuit a standard direct-writing electrocardiographic machine is employed. The connections to the patient and the record are made in the normal manner. A connection from the galvanometer coil allows the electrocardiographic voltage appearing there to be applied to the FM modulator unit. This FM modulator unit converts the low frequency voltage appearing across the galvanometer to a 1,250 cycle frequency modulated voltage. This is done by employing an oscillator whose frequency may be varied in direct response to another voltage. With no voltage across the galvanometer terminals, the frequency is normally at 1,250 cycles. With 1 millivolt positive voltage applied to the electrocardiographic machine input terminals, the displacement of the galvanometer is one centimeter upward. The voltage across the galvanometer terminals which are controlling the FM oscillator then causes the oscillator to deviate from its center frequency to 1,450 cycles or a deviation

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From the Cardiovascular Laboratory, Department of Medicine, University of Kansas Medical Center, Kansas City, Kan.

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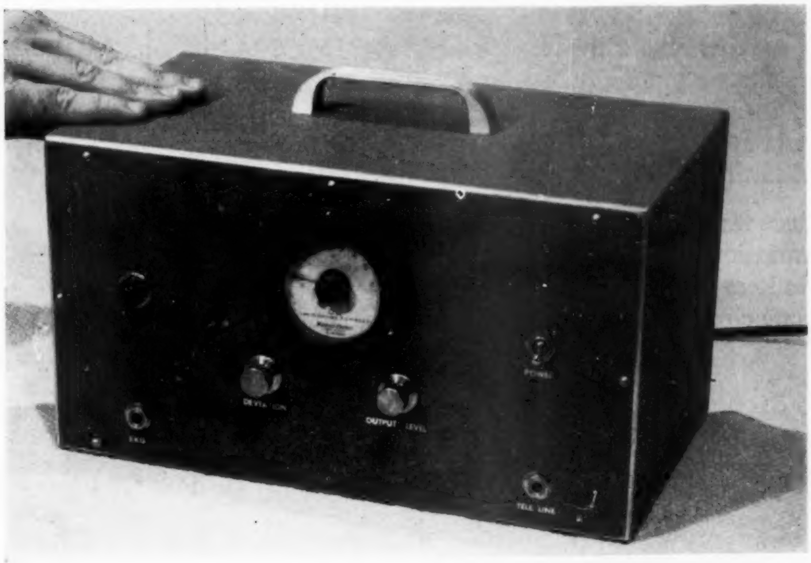

Fig. 1.—Transmitter.

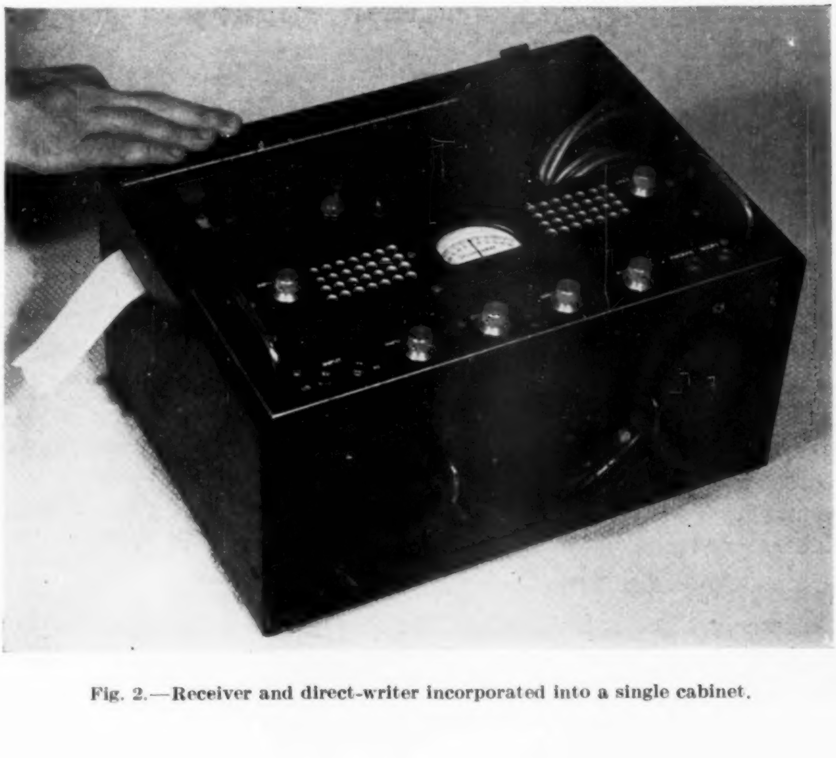

Fig. 2.—Receiver and direct-writer incorporated into a single cabinet.

of plus 200 cycles. Likewise a one millivolt negative voltage at the electrocardiographic input will cause the oscillator output to deviate 200 cycles downward. The output frequency of the oscillator is caused to deviate in a linear fashion in response to the input electrocardiographic voltage. This oscillator output is applied to the telephone terminals and at a level approximating the normal level of a standard telephone instrument.

Since the intelligence is carried by frequency variation rather than by amplitude variations, the voltage on the telephone line remains constant and no amplitude limiters are necessary to prevent overvoltage and resulting cross talk on the telephone circuits.

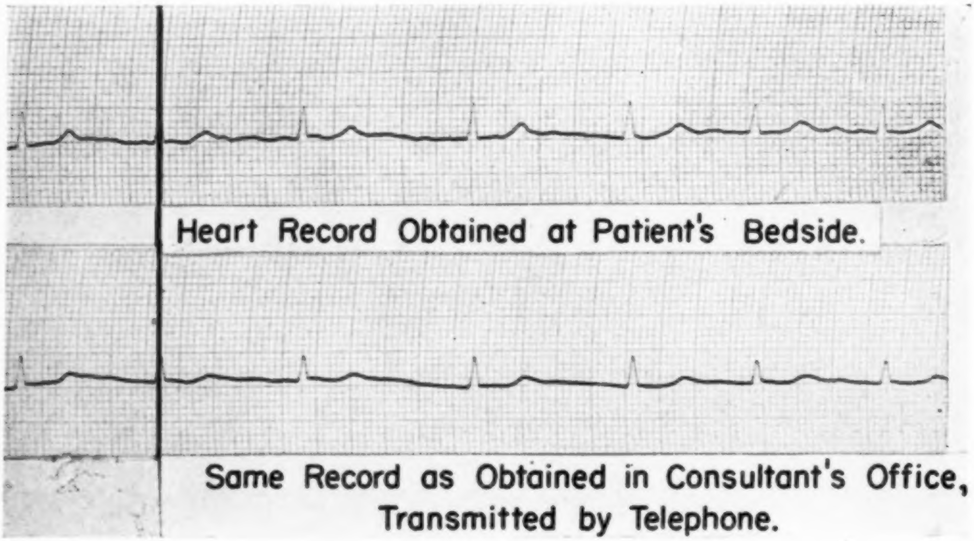

Fig. 3.

At the receiving terminal the frequency modulated voltage is amplified and applied to a discriminator. The discriminator converts the frequency variations to amplitude variations. The output then will be a voltage identical with that which appeared at the galvonometer terminals of the transmitting electrocardiographic machine. This voltage is applied to a galvanometer at the receiving terminal. The technical problems involved in the actual use are minimal. Any laboratory technician could use the equipment.

A sample electrocardiogram, transmitted from Lawrence, Kansas, to Kansas City, Kansas, a distance of 35 miles, is shown (Fig. 3). The telephone company servicing this area (Southwestern Bell Telephone) permits use of the telephone line at standard long distance rates.

CIRCUIT OPERATION FOR TELE-ELECTROCARDIOGRAPHIC TRANSMITTER

V_1, V_2, and V_3 are part of the power supply delivering +250, +150, and −150 volts for operation of the remainder of the circuit (Fig. 4).

V_5 is connected as a Hartley oscillator whose principal frequency determining components are a toroidal inductor and capacitors *A*. Values are such to obtain a frequency of approximately 30 kilocycles. Capacitors *A* are voltage sensitive, and capacity changes when DC or low frequency AC is applied across their terminals. A bias variable from 0 to −150 volts is applied to one terminal of each capacitor and a varying signal from an electrocardiographic galvanometer is connected across the other terminal.

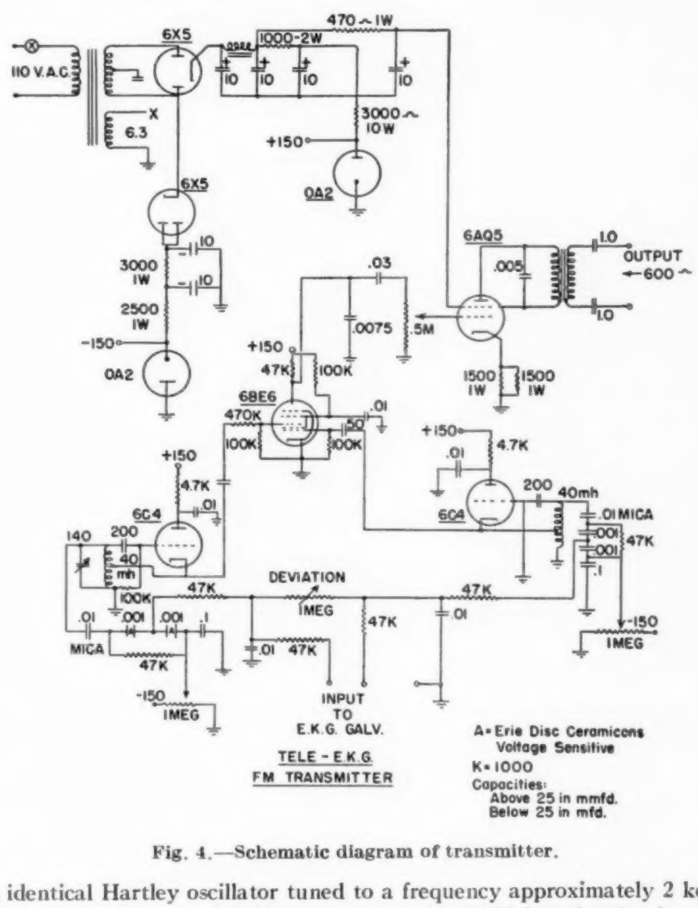

Fig. 4.—Schematic diagram of transmitter.

V_6 is an identical Hartley oscillator tuned to a frequency approximately 2 kc. higher than that of V_5. Bias is applied in an identical manner to that of V_5 but signal voltage is applied in opposite phase. Signal voltage input is approximately 150 volts DC above ground. With no signal input, the difference in frequency of the two oscillators is approximately 1,250 cycles but may be varied by means of an adjustable capacitor across one oscillator. With 5 volts of signal of one polarity applied to the input terminals the frequency of one oscillator increases by approximately 100 cycles and the other decreases by the same amount. The difference in frequency of the two oscillators is thus varied. A total peak-to-peak difference in frequency of 400 cycles results from a 10-volt peak-to-peak change in applied signal. Capacitors *A* are temperature sensitive but since the two oscillators tend to vary in the same direction the difference frequency tends to remain constant when temperature changes. Nonlinearity of frequency change with respect to applied signal voltage is also largely canceled due to push-pull signal connection.

V_7 is a mixer or modulator tube receiving the outputs of the two oscillators and generating the difference frequency. This audio output is filtered by an RC network to remove the higher frequency components.

V_8 is an audio amplifier delivering an output adjustable from zero to a maximum of one watt into a 600 ohm load. The high maximum output is provided for experimental work with magnetic coupling devices.

CIRCUIT OPERATION FOR TELE-ELECTROCARDIOGRAPHIC RECEIVER

V_5, V_6, and V_7 are part of power supply delivering +200, +150, and −150 volts DC for remainder of circuit (Fig. 5).

Input from the telephone line is an audio-signal frequency modulated by the electrocardiographic wave form. V_1 is an amplifier. V_2 is a cathode coupled clipper.

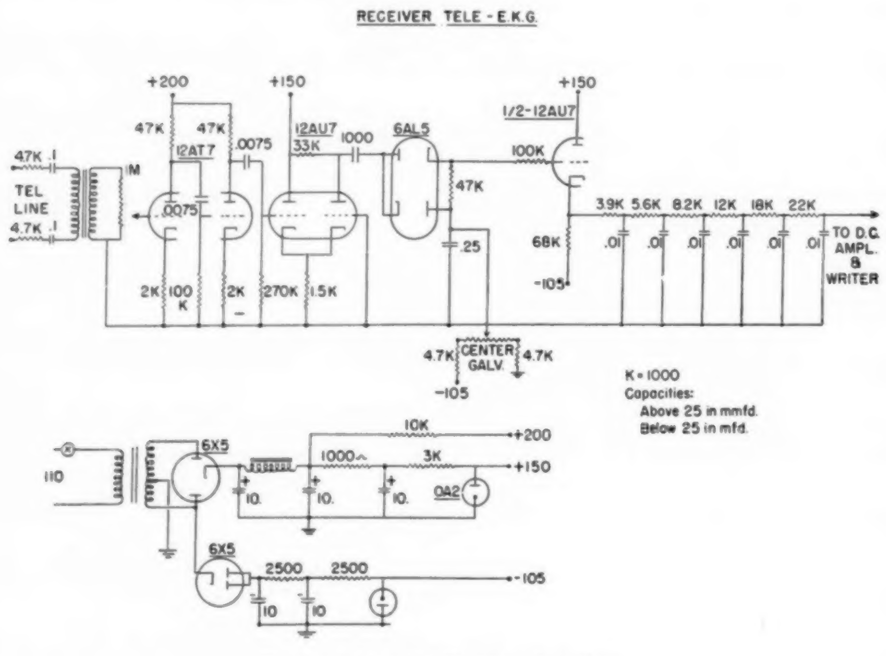

Fig. 5.—Schematic diagram of receiver.

The output wave form of V_2 is a rectangular wave constant in amplitude. This output is differentiated and rectified by V_3. The average value of this rectified wave is then proportional to frequency. V_4 is a direct coupled amplifier for the modulation frequency. Output of V_4 is integrated by an RC network. The output DC voltage varies around zero, negative for decreasing input frequencies and positive for increasing input frequencies. Output for modulating frequency is constant to approximately 50 cycles per second.

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Clinical Reports

MARFAN'S SYNDROME

MAXWELL ANDERSON, M.D., AND H. R. PRATT-THOMAS, M.D.

CHARLESTON, S. C.

MARFAN'S syndrome is probably more commonly known as arachnodactyly, but the widespread malformation of body structure is not well indicated by the term "spider fingers" (arachnodactyly). Marfan[1] first described the condition in 1896, and it remained a rarity in the foreign literature until Piper and Irving-Jones[2] first brought the syndrome, with its frequently associated congenital heart disease, to the attention of the American physician. Ophthalmologists quickly began reporting cases because of the frequent bilateral subluxation of the lenses and fully established the hereditary factor. Rados[3] reviewed the literature through 1939 and published a comprehensive report on 211 cases in 1942. General interest has mounted as indicated by recent articles in a variety of journals,[4-10] and the total number of cases reported in the literature is 349. A case is easily recognized, but just as easily missed if the physician is unaware of the syndrome and undoubtedly many are never suspected.

The characteristic findings of long thin fingers and toes with increased height, sparse subcutaneous fat and musculature, and relaxation of ligaments, dolichocephaly with odd features such as big ears, bossing of the frontal bones, and a high palate, funnel-shaped chest and kyphoscoliosis, bilateral subluxation of the lenses, and cardiovascular disorders are present in varying degrees.

More complete necropsies have shown an amazingly high incidence of significant cardiovascular disorders. Uyeyama and associates[9] and Tobin and associates[10] reviewed a total of fifteen necropsies and found twelve of these had cardiovascular lesions, seven of which were aortic. The lesions were similar in the latter cases and included cardiac hypertrophy, deformities of the aortic valve, dilatation of the aortic valve ring and varying degrees of dilatation of the sinuses of Valsalva and/or of the ascending portion of the aorta. Mural and valvular thickening, grossly resembling rheumatic lesions, were seen in each case. Microscopic studies did not show these to be of rheumatic origin. Carroll,[11] Lutman and Neel[12] and Lillian[13] reported additional necropsies. Carroll[11] simply states that his case had not been described before and showed "congenital heart disease" and "dissecting aneurysm," making this the fifth case of dissecting

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From the Departments of Internal Medicine and Pathology, Medical College of South Carolina, Charleston, S. C.

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aneurysm in the nineteen necropsies to date. Lutman and Neel[12] describe hypertrophy of the heart and dilatation of the root of the aorta with aortic and mitral valvular insufficiency but "no congenital abnormalities." These changes were explained on the basis of "chronic rheumatic endocarditis" and "mild generalized arteriosclerosis." It was not recognized until later that this was a case of Marfan's syndrome. Lillian[13] described in full the gross and microscopic findings but emphasized the saccular aneurysm of the pulmonary artery with patent ductus arteriosus and vegetative endarteritis, nonbacterial mitral valvulitis, and congenital pulmonary cysts. He incidentally mentioned that the patient had arachnodactyly.

Lillian's[13] description of an aneurysm of the pulmonary artery in a case of arachnodactyly is the first reported. It is probable that his microscopic findings of "focal as well as diffuse hyalinization of the media . . . focal collections of lymphocytes in the media . . . disruption and irregular distribution of the elastic lamellae in the proximal pulmonary artery with complete absence of elastic fibers in the aneurysm" are similar to the medial changes described by Baer and associates,[5] Etter and Glover,[6] Uyeyama and associates[9] and Tobin and associates.[10] The following case is worthy of presentation, since it demonstrates medial degeneration of the aorta and pulmonary artery with aneurysmal formation and incomplete rupture of the latter.

CASE REPORT

The patient, an unmarried 23-year-old Negro woman, was first seen at the Obstetrical Clinic of Roper Hospital in 1941. She was delivered in February, 1942, and was sterilized in May, 1942, because of congenital heart disease with borderline congestive heart failure. She was followed in the Medical Clinic and showed varying cardiac murmurs and was intermittently thought to have a congenital defect or active rheumatic heart disease. Her blood pressure varied from 90/0 to 130/60 mm. Hg; sedimentation rates from 6 to 41 mm. per hour and atrioventricular conduction time (P-R interval on electrocardiogram) from 0.20 to 0.34 second. The blood serology remained negative. In 1948, the patient was digitalized because of congestive heart failure and repeated admissions with decompensation followed because of inability of the patient to follow treatment instructions. Extensive studies including angiocardiography and cardiac catheterization revealed only progressive enlargement of the heart to the right and left with prominence of the pulmonary conus and a large dense right hilar shadow. Her last admission was in March, 1949, with extreme decompensation and failure to respond to treatment. The roentgenogram showed marked progressive enlargement of the heart especially to the right with a very large right ventricle and pulmonary artery. The pulmonary arteries in each conus were dilated and showed forceful pulsations. The radiologists felt that this was probably an interatrial septal defect with superimposed rheumatic valvular disease. The electrocardiogram showed evidence of strain of the left side of the heart until this admission when slight right-axis deviation (+98 degrees) with a P-R interval of 0.25 second was found. During this admission it was realized that the patient was arachnodactylic and fitted into Marfan's syndrome. Observers had noted previously that she "couldn't see well," was "underweight," was "only fairly well developed," "extremities are very thin and phalanges of hands and feet are long and slender," and "fingers are spider-like." She failed to respond to treatment and died in right-sided heart failure with a clinical diagnosis of patent ductus arteriosus and patent interatrial septal defect.

Necropsy.—This was performed 22 hours after death. The body measured 62 inches in length and weighed an estimated 100 pounds. The characteristic arachnodactylic abnormalities were as noted clinically. The chief interest centered about the heart and great vessels.

The heart weighed 650 grams. The greatest transverse diameter was 17 cm. The epicardium and endocardium were smooth and glistening. The valve diameters were as follows: tricuspid valve, 12.3 cm.; pulmonary valve, 9.5 cm.; mitral valve, 10.5 cm.; aortic valve, 6.5 cm. The myocardium was of dull reddish-brown color and firm consistency. There was marked hypertrophy of the right ventricle whose wall averaged 13 mm. in thickness and it exhibited very prominent, stout papillary muscles. Its chamber was moderately dilated. The left ventricle was moderately hypertrophied, and its wall measured 16 mm. in thickness. There were no valvular defects. The coronary ostia were of normal size and nonobstructed, and the coronary arteries had thin pliable walls with widely patent lumina. Above the pulmonary valve there was a fusiform dilatation of the pulmonary artery (Fig. 1). The inside circumference estimated with the greatest diameter of this dilatation measured 11.5 cm. A transverse rent was present in the lining of the pulmonary artery which measured 5 cm. in length and had L- and V-shaped radiations at either end (Fig. 1). Six centimeters above the pulmonary valve the pulmonary artery communicated with the aorta by means of a patent ductus arteriosus one centimeter in diameter.

Fig. 1.—Fusiform dilatation of pulmonary artery with 5 cm. rent extending partially through its wall.

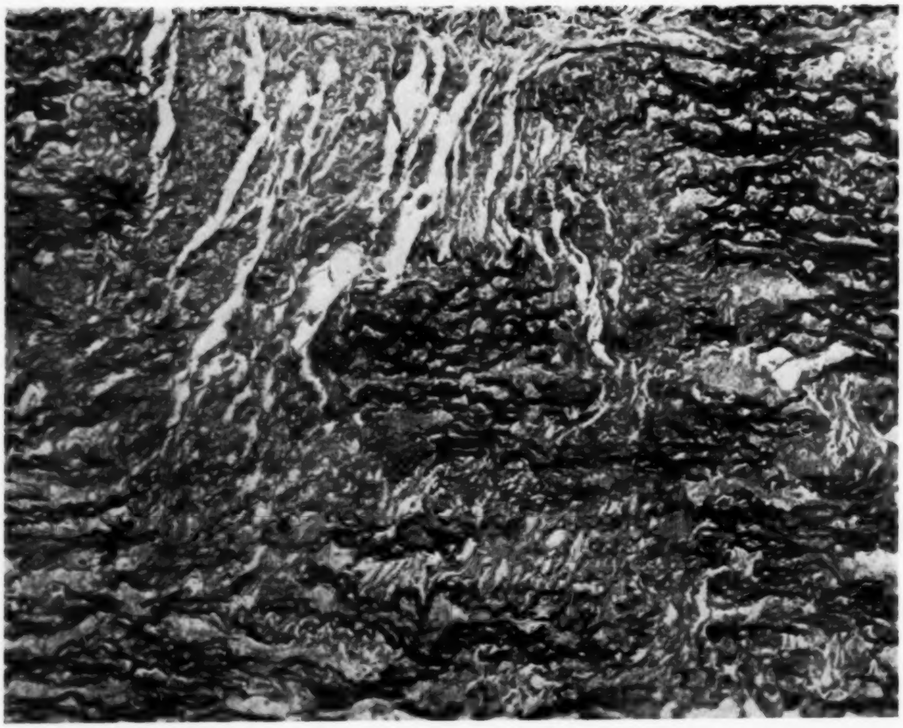

Fig. 2.—Profound fragmentation and loss of elastic fibers in the media of the pulmonary artery with increase in ground substance. Verhoeff's elastic tissue stain × 150.

Fig. 3.—Section through incomplete rupture of pulmonary artery showing thinning of media with loss of elastic fibers. Verhoeff's elastic tissue stain × 25.

There was moderate atheromatous involvement of the dilated pulmonary artery from the pulmonary valve to the patent ductus arteriosus. There was minimal atherosclerosis of the aorta immediately above the aortic valve. The remainder of the aorta presented a smooth pliable intima with patent openings in the major arteries.

Microscopic findings showed hypertrophy of the cardiac muscle cells throughout the myocardium. In some areas there was degeneration with a granular and vacuolated appearance of the cytoplasm and a moderate amount of interstitial fibrosis. An organizing thrombus was found in the right auricle. Sections of the coronary vessels failed to show any degenerative changes. The elastic fibers of the media of the pulmonary artery were coarse, irregular, and fragmented. Between the fibers there were accumulations of pale, staining mucoid or finely fibrillar ground substance. This accumulation of material reached cystic proportions, and in many areas only fragmentary islands of elastic fibers remained (Fig. 2). Sections through the incomplete rupture revealed marked thinning of the media with virtual disappearance of the elastic components (Fig. 3). The adventitia overlying the defect showed some fibrous tissue reaction. Sections of the aorta showed pooling of ground substance with loss of elastic fibrils simulating the appearance of the pulmonary artery (Fig. 4).

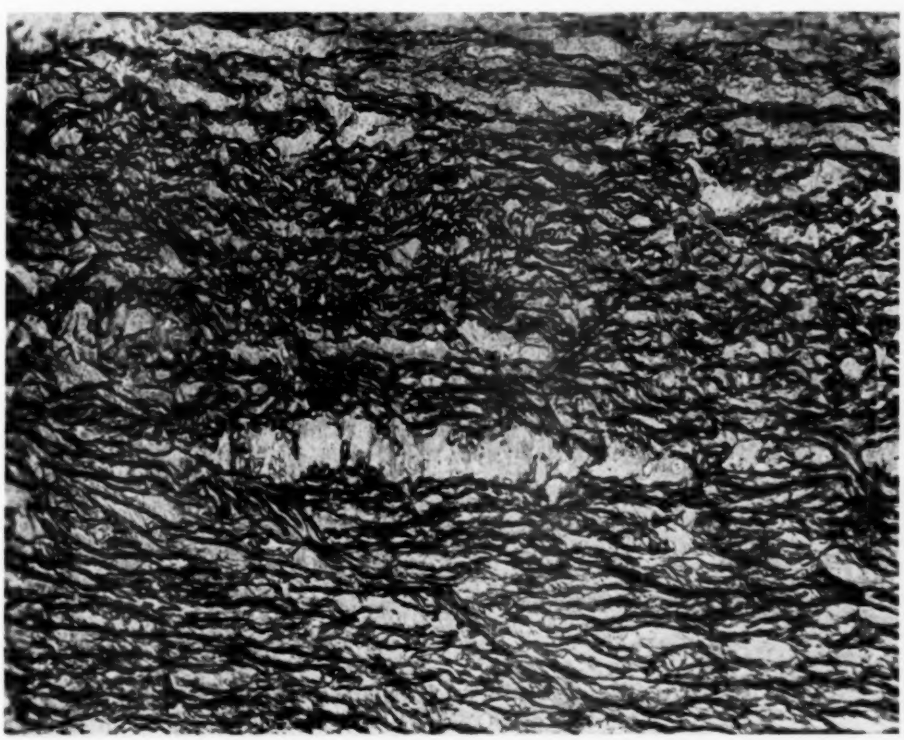

Fig. 4.—Media of aorta showing coarse, irregular elastic fibers with areas of cystic degeneration. Verhoeff's elastic tissue stain × 150.

DISCUSSION

It is of interest that the patient's daughter is also arachnodactylic. No definite history is obtainable about the rest of the family. The child, followed in the Pediatric Clinic at Roper Hospital since birth, has shown recurrent purulent conjunctivitis and dacryocystitis probably due to congenital atresia of the

lacrymal duct. At two months, it was noted that the baby had a "peculiar shape with large head and looks malnourished." At six months, she was "malnourished with wasted extremities, as is true of the body as a whole." At 4 years of age a systolic murmur at the apex of the heart was heard, and it was noted that the patient was "underweight and doesn't appear to have enough power in legs to move about unaided—although walks fairly well unassisted. There is some bossing of the skull and poor musculature of the extremities with marked looseness of joints." The patient was also followed in the rheumatic fever clinic and roentgenogram showed cardiac enlargement with prominence of the right hilum and slight bulging of the pulmonary conus. There was also a rounded bulging above the right hilum and an area of translucency in the left apex. The radiologists could not decide if this was rheumatic or congenital heart disease but felt that the mass above the right hilum was a tuberculous lymph node. Clinically, the patient was thought to have rheumatic heart disease or congenital heart disease, and it was never recognized clinically that she had Marfan's syndrome. It is reported that she is hospitalized in New York.

The present case is the nineteenth necropsy report on a case of Marfan's syndrome. All of the four cases reported since Tobin's[10] review, (Table I), have abnormalities of the great vessels, making a total of eleven of nineteen necropsied

TABLE I. AUTOPSY FINDINGS (4 CASES SINCE TOBIN)

AUTHOR	SEX AND AGE AT DEATH (YEARS)	ANATOMIC FINDINGS (NOT RELATED TO HEART AND AORTA)	HEART AND AORTA
Carroll[11]	Man 12	Ectopia lentis, arachnodactyly, calcified astrocytoma.	"Congenital Heart Disease" "Dissecting Aneurysm."
Lutman and Neel[12]	Man 37	Kyphoscoliosis, reduced anteroposterior diameter of chest, congestion of liver.	Hypertrophy of heart; dilatation of root of aorta; chronic rheumatic endocarditis of aortic and mitral valves; aortic and mitral insufficiency; myocardial fibrosis and degeneration; thrombosis of right auricular appendage; mild generalized arteriosclerosis; areas of endocardial thickening.
Lillian[13]	Woman 17	Congenital pulmonary cysts, mycotic aneurysms of the peripheral pulmonary arterial radicals, pulmonary infarcts, focal embolic glomerulonephritis, hemothorax, left.	Hypertrophy of heart; saccular aneurysm of pulmonary trunk; nonbacterial mitral valvulitis; patent ductus arteriosus with vegetative endarteritis.
Anderson and Pratt-Thomas	Woman 23	Pneumonia, acute, lobular, chronic passive congestion of liver.	Hypertrophy of heart; aneurysm of pulmonary artery with medial degeneration and rupture, incomplete; mural thrombosis; fibrosis and degeneration of myocardium.

cases with lesions of this nature. This figure is highly significant when it is realized that five of the other eight were under 28 months of age, while these eleven were 14 to 37 years of age.

It is also emphasized that the lesions grossly resembling rheumatic changes in the cases of Lutman and Neel[12] and Lillian[13] do not prove to be so microscopically. The cardiac lesions of Marfan's syndrome probably are due infrequently to rheumatic heart disease in spite of repeated clinical difficulty in differential diagnosis.

The medial degeneration observed in our case is similar to that described by the recent writers listed in this paper. Demonstration of this change with aneurysmal formation and intimal tearing in the pulmonary artery adds to the increasing knowledge of the manifestations of Marfan's syndrome.

SUMMARY

A case of Marfan's syndrome exhibiting medial degeneration and aneurysmal formation with incomplete rupture of the pulmonary artery is reported with a review of the literature.

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ELECTROCARDIOGRAPHIC CHANGES AFTER QUINIDINE IN SUPRAVENTRICULAR TACHYCARDIA

Simulation of Acute Myocardial Infarction

Marcus A. Rothschild, M.D., and Seymour Furman, M.D.

New York, N. Y.

THE electrocardiographic changes produced by quinidine and rapid heart action are well known. The purpose of this communication is to report an unusual electrocardiographic finding, the simulation of acute myocardial infarction in a patient who had supraventricular tachycardia and who was treated with quinidine. This phenomenon has not been previously reported.

CASE REPORT

T. B., a 61-year-old white woman, was first admitted to the medical service of Beth Israel Hospital in May, 1947, complaining of severe pressing precordial pain for four hours. Asymptomatic hypertension had been present for the previous eight years. During the winter of 1946 she had noted tight squeezing chest pain on exposure to cold. For the ten days preceding admission there had been daily, sharp, sticking precordial pains.

Past history revealed gastrointestinal episodes of sharp right upper quadrant pain since 1940, associated with nausea and vomiting. Jaundice had been present during one of these attacks.

Physical Examination.—The patient was a well developed, well nourished white woman lying flat in bed, complaining of chest pain. Temperature 100.4° F., pulse rate 45 and regular, respiration 20 per minute, blood pressure 150/90 mm. Hg. The skin was normal. Examination of the eyes revealed: sclera clear, pupils reacted to light and accommodation. The fundi were within normal limits. The neck was supple, the veins were not distended, and there was no adenopathy. The lungs were normal to percussion and auscultation. The heart was enlarged to one centimeter outside the left midclavicular line. The sounds were faint; no thrills or murmurs were present; the second aortic sound was louder than the second pulmonic sound. Abdominal examination disclosed a firm liver 2 cm. below the right costal margin. The extremities appeared normal and there was no edema.

Laboratory Findings.—Routine urine analysis was normal. The blood count showed 11.5 Gm. hemoglobin per 100 c.c., 12,200 leukocytes per c.mm., of which 74 per cent were polymorphonuclears, 22 per cent lymphocytes, and 4 per cent monocytes. The erythrocyte sedimentation rate (Westergren) was 10 mm. per hour and during the first four weeks it rose to 50 mm. and fell at the end of six weeks to 22 mm. per hour.

The initial electrocardiogram (Fig. 1,*A*) revealed atrial fibrillation with runs of sinus rhythm and first degree atrioventricular block. There was a 2 mm. elevation of the S-T segment in Leads II and III and a 6 mm. inversion of T in Lead III.

She was treated with bed rest, sedatives, oxygen, penicillin and Dicumerol. Her course was complicated by changes in the atrial rhythm and ventricular rate. Initial electrocardiograms showed Wenckebach periods, and later atrial fibrillation with a slow ventricular rate. Subsequently, the cardiac rhythm became normal without specific therapy and after six weeks she was

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From the Cardiographic Laboratory and Medical Service of Beth Israel Hospital, New York, N. Y.
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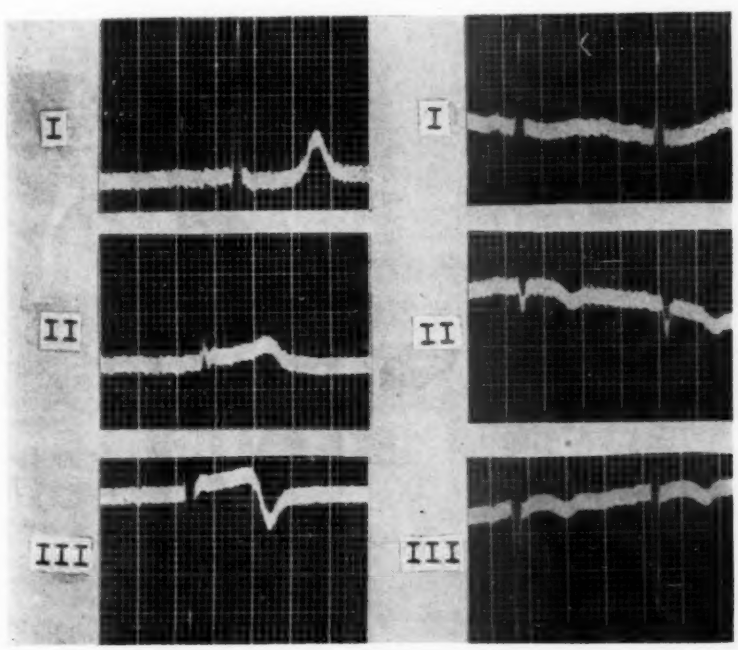
discharged asymptomatic without any evidence of cardiac failure. Serial tracings revealed evolution of the electrocardiographic changes compatible with posterior wall myocardial infarction (Fig. 1,*B*).

The patient was readmitted one year later because of the recurrence of right upper quadrant pain. There was evidence of cholelithiasis and a small hiatus hernia on roentgenogram. She was treated conservatively, given a low fat diet, and discharged improved after two weeks. The electrocardiogram was the same as on the previous admission.

In 1951 she was admitted for the third time because of attacks of hunger and dizziness. A glucose tolerance test revealed four- and five-hour blood sugar values of 68 mg. and 57 mg. per 100 c.c., respectively. She was placed on a high protein diet and discharged improved after two weeks.



A. *B.*

Fig. 1.—A. (5-5-47) The first tracing showing an inverted T_3. Initial R_3 equals 0.2 mm. (See text.) *B.* (6-11-47) Serial changes of a posterior wall myocardial infarction.

On the morning of her present and fourth admission, the patient was seen in the medical clinic for routine examination. She was comfortable and unaware of any irregularity in her heartbeat. During the six years since her first admission there had been no dyspnea, edema, cyanosis, cough, or hemoptysis. Angina pectoris occurred only rarely, and since her last admission, her gastrointestinal complaints were minimal. Heart rate was 100 and irregular, and an electrocardiogram showed atrial flutter (Fig. 2) and the patient was admitted to the hospital for control of the arrhythmia.

On physical examination she did not appear ill. Temperature was 100° F., respiration 18 per minute and blood pressure 150/90 mm. Hg. Examination of the head revealed no abnormalities. The eyes appeared normal and funduscopic examination revealed slight narrowing of the arteries with an increased light reflex. The neck veins were not distended, but prominent "a" waves were noted. The lungs were normal to percussion and auscultation. Her heart was enlarged to 2 cm. outside the left midclavicular line; the sounds were of normal intensity and dura-

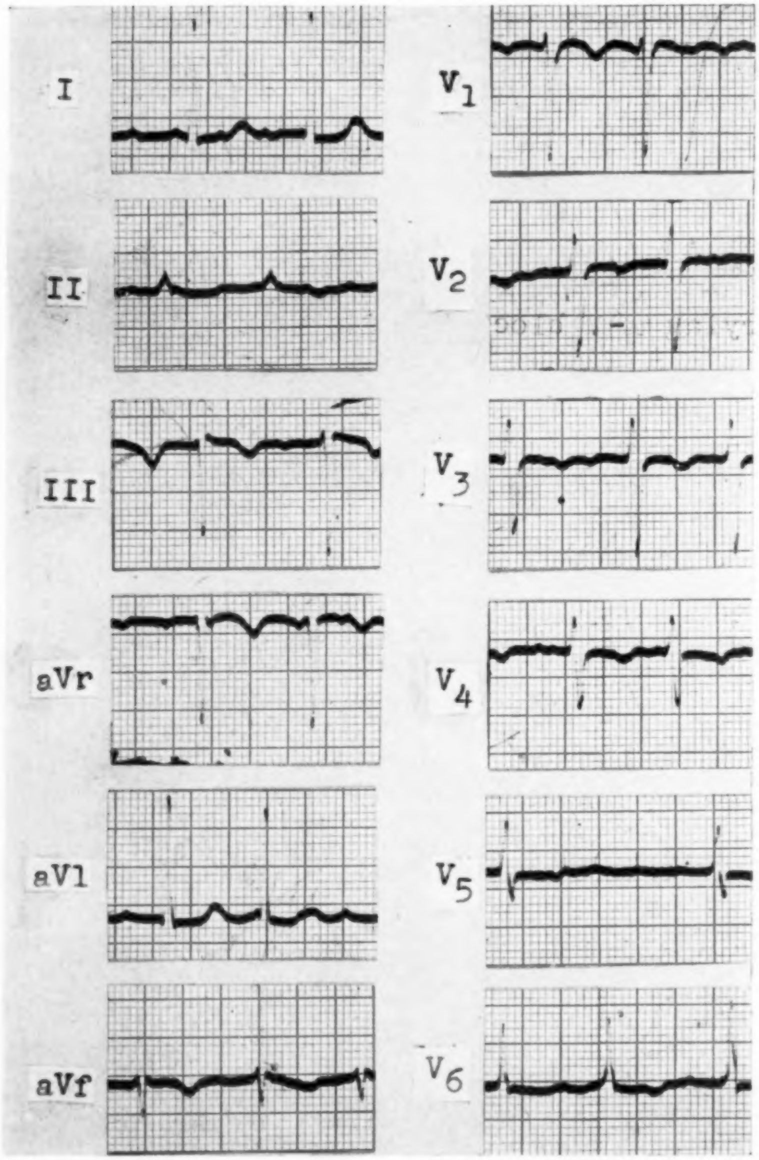


Fig. 2.—(2-13-53) The initial tracing on the patient's fourth admission. Atrial flutter, rate 260 per minute; ventricular rate 90 to 100 per minute. There is inversion of the T waves in Leads III and aV_F.

tion; the second aortic sound was louder than the second pulmonic sound; no thrills or murmurs were noted. No abnormal organs or masses could be palpated in the abdomen. There was no edema of the extremities; the dorsalis pedis pulsations were normal.

Laboratory Findings.—The routine urine examination was within normal limits. Complete blood count revealed 3.22 million red blood cells per c.mm., 10.5 Gm. of hemoglobin per 100 c.c., 4,800 leukocytes per c.mm., and a normal differential count.

The erythrocyte sedimentation rate was 11 mm. in one hour (Westergren). The fasting blood sugar was 101 mg. per 100 c.c., and a glucose tolerance test now showed values of 58 mg. per 100 c.c. at four and one-half hours with a rise to 96 mg. per 100 c.c. at five hours. The non-protein nitrogen was 37 mg. per 100 c.c. The basal metabolic rate was plus five and plus seven. An enlarged cardiac silhouette was seen on roentgenogram.

Though procaine amide in our hands has only rarely been helpful in converting atrial flutter,[1] this drug was given in an attempt to correct the arrhythmia. An oral dose of 750 mg. was administered every six hours for eighteen hours. No change in the original flutter rate or atrioventricular conduction occurred. Quinidine therapy was started on Feb. 14 with 0.2 Gm. of quinidine sulfate orally every two hours for four doses. No effect on the cardiac rate was seen. On Feb. 15, after 0.2 Gm. initial dose, 0.3 Gm. was given every two hours for three doses to a total dose of 1.1 Gm. over an eight-hour period. A small decrease in the flutter rate from 270 to 240 per minute occurred. The ventricular response remained the same. On Feb. 16, quinidine therapy was continued, 0.3 Gm. at 10:30 in the morning and 0.3 Gm. every hour thereafter. There was no change in either rate or rhythm until 3:30 P.M., one hour after a total of 1.5 Gm. had been ingested. The flutter rate had been reduced to 170 per minute (Fig. 3) with a ventricular response of 80 to 90 per minute. Another 0.3 Gm. was given at 3:30 P.M. and the time interval between dosages lengthened to two hours. At 5:30 P.M. an electrocardiogram revealed a fall in atrial rate to 150 per minute, with a frequent one-to-one ventricular response (Fig. 4). Reciprocal S-T depression and elevation in Leads I and III, respectively, were observed. Another 0.3 Gm. was given at this time, totaling 2.1 Gm. in seven hours, and at 7:30 P.M., two hours later, the electrocardiogram revealed striking changes (Fig. 5,*A*). A five millimeter Q wave with 3 mm. S-T segment elevation in Leads III and aV_F appeared and S-T segment depression in Leads I, aV_L and V_3, V_4, V_5, and V_6. The atrial flutter rate remained 150 per minute with a persistent one-to-one ventricular response.

In spite of these electrocardiographic changes characteristic of an acute posterior wall myocardial infarction, the patient experienced little discomfort, and complained only of a feeling of rapid heart beating. She was not apprehensive, had no chest pain, and there was no evidence of congestive heart failure. Quinidine therapy was discontinued and she was given 75 mg. of Demerol. During the next five hours the ventricular rate fell to prequinidine levels of 100 per minute and the electrocardiogram (Fig. 5,*B*) was the same as on admission. During the next three weeks the patient was observed for clinical evidences of myocardial infarction. There were none. Temperature was between 99° F. and 100.6° F. during the first few hospital days and continued about the same throughout her whole three-week hospital course. There was no elevation of erythrocyte sedimentation rate or leukocytosis. On the seventh hospital day an attempt to break the atrial flutter with rapid intravenous digitalization, using 1.2 mg. of Cedilanid failed, and the patient was then redigitalized with 1.2 mg. of digitoxin orally with the plan to maintain her on digitoxin. On the following morning 0.1 mg. of digitoxin was given. The next day a bout of atrial fibrillation occurred, followed in a few hours by regular sinus rhythm (Fig. 6,*A*). Digitoxin was discontinued and quinidine 0.2 Gm. was given and repeated once in four hours. However, severe diarrhea and ringing in the ears ensued and this drug was stopped. The next morning atrial flutter was again present with a flutter rate of 180 per minute and a ventricular rate of 60 to 70 per minute (Fig. 6,B). Digitoxin 0.2 mg. daily was prescribed as a maintenance dose, and the patient was discharged asymptomatic, afebrile, and physically about the same as on admission three weeks before.

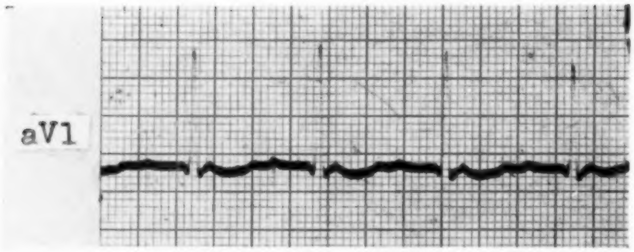


Fig. 3.—(2-16-53; 3:30 P.M.) After 1.5 Gm. of quinidine sulfate, atrial flutter rate 170 per minute. (See text.)

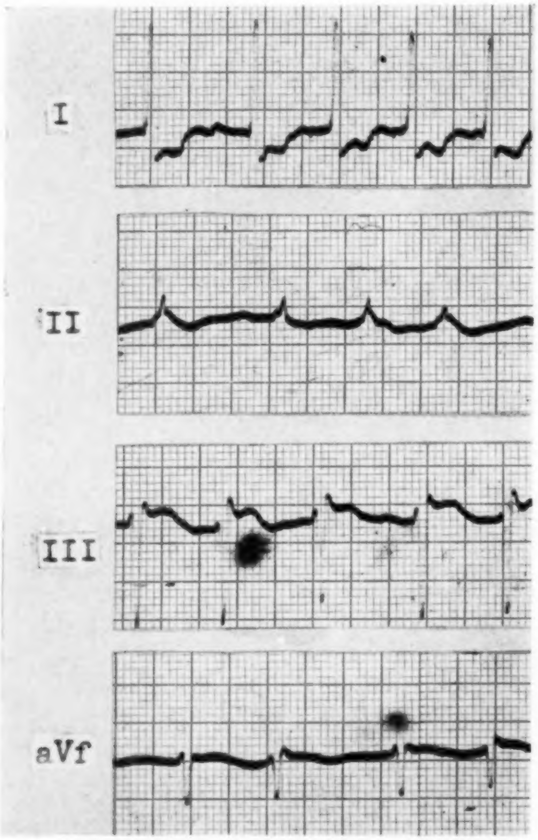
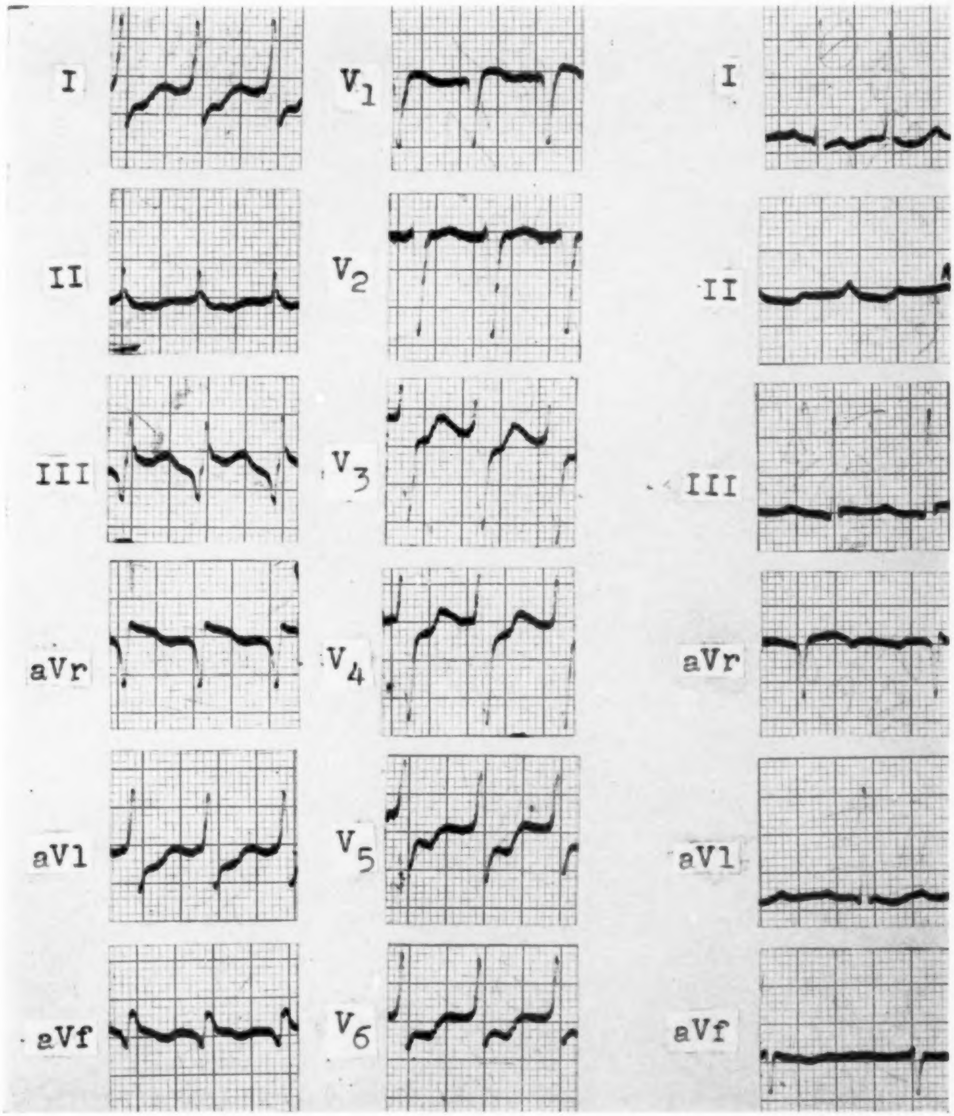


Fig. 4.—(2-16-53; 5:30 P.M.) After 1.8 Gm. of quinidine sulfate. There is a decrease in the flutter rate to 150 per minute with frequent one-to-one ventricular response. Note that the R waves of the rapid beats nearly disappear (Lead III).

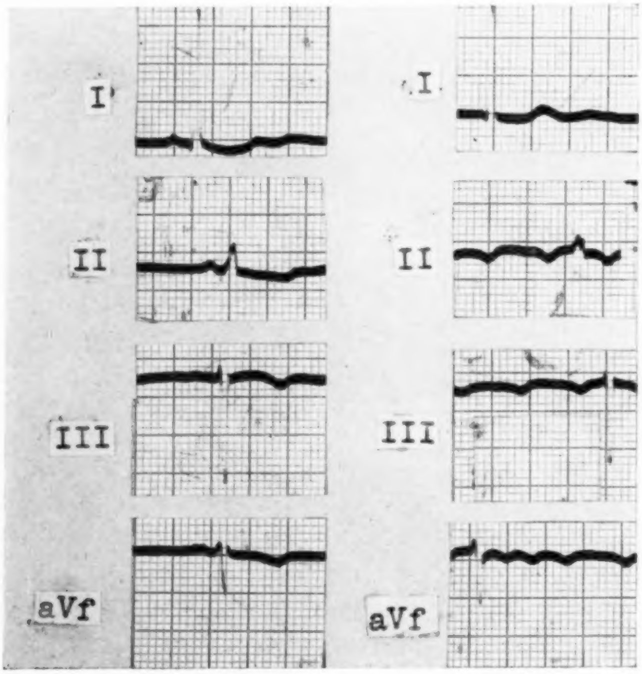


A. *B.*

Fig. 5.—*A*. (2-16 53; 7:30 P.M.) After 2.1 Gm. of quinidine sulfate. The atrial flutter rate is 150 per minute with a persistent one-to-one ventricular response. There is a deep Q wave in Leads III and aV_F with S-T segment elevation in these leads and S-T segment depression in Leads I, aV_L, and V_3, V_4, V_5, V_6. *B*.—(12:30 A.M.) Tracing taken five hours after *A* showing complete reversal of the previous electrocardiographic signs of acute myocardial infarction. (See text.)

The unusual transient electrocardiographic changes in this patient are difficult to explain. Three important factors must be considered.

1. The patient had previously sustained a posterior wall myocardial infarction in 1947 with major abnormalities in Lead III, and the present changes are similar to those.



A. *B.*

Fig. 6.—*A.* (2-28-53) Tracing showing regular sinus rhythm after digitalization. *B.*—(3-1-53) one day later; patient still on digitoxin, atrial flutter again present. No significant changes from admission electrocardiogram.

2. Quinidine has been reported to cause many electrocardiographic changes. The P waves are widened, P-R interval prolonged as is the QRS which may be 0.12 second or greater. The T waves are notched, depressed or inverted, and the Q-T interval or electrical systole is prolonged. In large doses toxic manifestations present themselves as atrioventricular block, bundle branch block, ventricular tachycardia and fibrillation. Complete cardiac arrest can occur.[2,3] Diamondstone and associates[4] have suggested, after observing retinal artery spasm in a case of quinine poisoning, that similar spasm could occur in the coronary vessels, thus producing ischemia. Foster and Layman[5] have recently reported a case of urticaria occurring after treatment with cinchophen, salicylates and iodides in which there developed signs of complete atrioventricular dissociation, and prominent Q waves in Leads II and III with S-T segment elevation and T-wave inver-

sion. The ventricular rate was 50 per minute. An electrocardiogram taken two weeks later had returned to normal. These authors postulated that a temporary or functional myocardial ischemia had been present. In our case the acute electrocardiographic changes occurred two hours after the last dose of quinidine, and these changes disappeared after seven hours. Lewis and associates[6] and recently Wegria[7] have shown that a maximal effect on the fibrillating rate occurs two hours after a single dose of quinidine and that some effect will still be present eight hours later. Our findings would correspond with this time sequence.

3. The third factor is the tachycardia. Previously, S-T segment depression, inversion of the T waves and prolonged Q-T intervals have been reported during and after cessation of paroxysmal tachycardias.[8,9]

There are three possible explanations for these sudden and reversible electrocardiographic findings. First, an actual fresh posterior wall myocardial infarction could have occurred. In the light of the rapidity of reversal of the electrocardiogram and the patient's subsequent clinical course this seems remote. Second, for technical reasons the tachycardia per se could have obscured the initial R wave. At 5:30 P.M. the electrocardiogram revealed a rapid ventricular rate approaching 150 per minute. As can be seen (Fig. 4), the small initial R wave of the rapid beat, 0.01 to 0.02 second, becomes reduced in size or even disappears. This may be due to the fact that at 50 to 100 cycles per second the frequency response of the galvanometer falls off substantially. The variations in the S-T segment may have resulted from either the tachycardia or the quinidine. Third, the development of ischemia due to an increased ventricular rate with a decreased cardiac output or due to direct effect of quinidine in the subnormal area of muscle around the old infarction could also explain the electrocardiographic changes.

The appearance of the Q wave in this case has not been fully explained. Necrosis of the myocardial tissue, not merely injury, is generally believed necessary for the production of a significant Q wave. The rapid appearance and disappearance of the Q waves in this patient, and the absence of clinical evidence of fresh myocardial necrosis suggests that other mechanisms for this abnormal wave must be considered.

SUMMARY AND CONCLUSIONS

1. During the treatment of atrial flutter with quinidine, the electrocardiographic findings typical of a posterior wall myocardial infarction with deep Q waves were observed which lasted for only five hours. The presence of this Q wave poses a question as to the relationship between the Q wave and myocardial necrosis.

2. The possible etiologic factors for these changes are discussed.

3. Though electrocardiographic changes after quinidine said to simulate acute myocardial infarction have previously been published, the appearance of deep Q waves has not been reported before.

The authors wish to express their appreciation to Dr. Harry Vesell for his constructive criticism and advice in the preparation of this material.

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Review of Meeting

REVIEW

FOURTH INTER-AMERICAN CONGRESS OF CARDIOLOGY, BUENOS AIRES, ARGENTINA, 1952

Part III

PEDRO COSSIO, M. D., AND HECTOR CAUL, M. D.
BUENOS AIRES, ARGENTINA

ELECTROCARDIOGRAMS

185. Autopsies were performed in twenty cases of valvular disease and the electrocardiographic interpretations were reviewed and found correct in most instances, proving their usefulness in clinical diagnosis.

186. Electrocardiographic alterations and photoplethysmographic arteriolar changes are induced by trophoenzymatic drugs such as ion exchange resins, K and Mg, respiratory enzymes, vitamin B complex, cytochrome C. Myocardial extracts, bile salts, adrenergic and colinergic mediators, and histamine are used to try to establish the extent of myocardial damage. In the less advanced cases of myocardial infarction the damages are reversible. Functional myocardial metabolic disturbances can be diagnosed in this manner.

187. The incidence of Master's two-step exercise on the electrocardiogram was reported: (1) Individuals with hypertension or angina pectoris with a previous normal or almost normal electrocardiogram which was much more influenced by tachycardia than by increase in either the systolic or diastolic blood pressure. Hypertension induced by exercise counter-balanced to a certain extent the coronary insufficiency brought on by tachycardia. (2) Angina pectoris cases with hypertension showed fewer changes than plain angina pectoris without hypertension.

EXPERIMENTAL ELECTROCARDIOGRAMS

188. All theories advanced on the mode of activation of the heart muscle in the process of contraction are based on indirect evidence such as electrical phenomena found on the epicardial or endocardial surface of the heart. A method for the study of the electrical phenomena in the muscle itself is described and shows that the electric activation progresses almost instantaneously from the endocardial surface to a certain depth in the myocardium (about 6 mm.) which corresponds to the penetration of the Purkinje system into the myocardium, and from there on the progress is much slower as it follows the myocardial fibers. Epicardial and auricular activation was considered, and the findings in the latter did not coincide with the present theories.

189, 190. In dogs procaine amide in massive but nontoxic doses decreases the speed of conduction in the free ventricular muscular zones adjacent to the epicardium but is noneffective on the subendocardial zones unless toxic dosages are used. (Purkinje muscular blockage). Even then, bundle branch block cannot be induced although peripheral leads suggest it, but the intrinsic deflection is greatly delayed in both ventricles. The delay in the septum is at the level of the transition from Purkinje's system to the muscular fibers. Only in rare instances can a Purkinje block (delay of conduction in the endocardial surface) be induced. The activation of the free walls is upward and from the endocardium to the epicardium at a speed of 4 meters per second on the endocardial surface, while on the epicardium of the left ventricle the speed of propagation is 300 to 400 mm. per second; it is slightly higher in the right ventricle. This agrees with Lewis and Harris' work. Bundle branch section does not alter the direction, speed, or sequence of the impulse in the free ventricular walls although there is a delay in the corresponding ventricle. The manner in which the epicardial impulse is transmitted differs from that generally accepted.

191, 192. Epicardial tracings were registered in six individuals with open epicardium and normal hearts in the course of intrathoracic surgery. Direct leads on different points of the right ventricle always showed rS complexes while in the higher portions of the left ventricle qR patterns were found and at other levels qRs curves. Probably the stimulus is not distributed as a uniform wave but spread through both ventricles from apex to base as proved by the relation R/S and the time measurement of the beginning and ending of the intrinsic deflection. There is an almost simultaneous spread of stimulus in the right ventricle proved by the very small topographic difference in opposition to what happens in dogs.

193. Acute pulmonary edema with closed chest (Luisada's method) was induced in anesthetized dogs by injecting one liter of physiologic saline at the distal end of each carotid; an autopsy followed to confirm this production. Electrocardiograms showed in the course of the injection a low P in all leads, an increased R with small S in left ventricular leads and transitory changes of ST-T. When the clinical signs of the acute pulmonary edema appeared curves corresponding to subendocardial lesion and ischemia of the left ventricle were seen.

194. Experimental hyperpotassemia was induced in anesthetized dogs by KCl and metabolic acidosis by NH_4Cl, corrected later by hypertonic glucose solution and insulin in the former and by sodium lactate in the latter. A close relationship was proved between the fall of the alkaline reserve and the increase of the extracellular potassium and an opposite situation in alkalosis.

195. An experimental study on dogs under Nembutal anesthesia was performed inducing fast and slow hydropericardium and hemopericardium and tracings under different conditions were registered.

196. Aortic stenosis induced in dogs below the origin of the left subclavian artery altered the voltage of the ventricular complexes, the initiation of the intrinsic deflection and the manner in which the activation wave progressed.

197. An experimental study in dogs with direct tracings at the interventricular septum is reported. The activation at this level is from left to right and from downward to upward at a speed of 1,000 to 1,200 mm. per second suggesting that the Purkinje branches penetrate deeply at this level. Right bundle branch block does not change the activation of the left ventricular septal zone, but left bundle branch block when marked inverts the activation of the same zone which also slows down to about 360 mm. per second. The delay in the transmission of the activation wave is in a small zone (1.5 to 2 mm.) near the right surface of the septum and happens when the impulse passes to the side that is blocked from regions activated by the nonblocked branch. This would simply imply that both branches are independent and eliminates the possibility of a connection between them.

198, 199. Conduction disorders are easily induced by digitalis or anoxia in the chicken's heart and the blockage may be: (1) sinoauricular, (2) interauricular (occasionally with monoauricular fibrillation), (3) auriculoventricular, (4) interventricular. Another paper deals with the same subject and the propagation of the stimulus in the heart of the *Bufo-arenarum*.

172, 173. In dogs progressive pulmonary stenosis was attained with a cellophane band and direct epicardial tracings were registered; four months later at reoperation right ventricular hypertrophy was observed and the epicardial tracing showed an increased amplitude of R in relation to S at the trabeculated zone and occasionally a delay of the apex of R in relation to the origin of QRS. Pressure readings are discussed.

BALLISTOCARDIOGRAM

200, 201, 202, 203, 204. A new model ballistocardiograph of lower cost and greater sensibility is described. This instrument records the body movements produced by the passage of blood from the heart to the peripheral resistance and may give a rough idea of the functional capacity of the heart. Typical ballistocardiograms are obtained in coarctation of the aorta and abnormal ones in arterial hypertension, cor pulmonale, and other conditions. Its value would be in borderline cases of coronary heart disease in 80 per cent of which abnormalities such as late downstroke, early M, and late M appear.

205, 206. It is attempted to correlate the ballistocardiogram with other graphic records of cardiac activity such as electrocardiogram, phlebogram, and phonocardiogram central pulse in normal and pathological conditions.

207, 208, 209, 210. The combined use of the discriminative precordial leads and Dock's electromagnetic ballistocardiograph is advocated for an early diagnosis of coronary insufficiency and as a complementary cardiological examination for diagnostic purposes and appraisal of the efficacy of drugs.

Another paper concludes that the ballistocardiogram is in no way a substitute for the electrocardiogram in the diagnosis of coronary disease, although as a rule individuals with abnormal electrocardiograms show marked alterations (Grade 3 or 4 of Brown's classification) in their ballistocardiogram.

211. The ballistocardiogram may be used to detect nicotine sensitivity in cardiovascular disease. The most common pictures were: (1) hyperkemic response when there were palpitations or neurocirculátory asthenia was suspected; (2) low HIJ and deep K in individuals with labile or sustained hypertension; (3) increased respiratory amplitude in subjects with coronary disease and nicotine angina. These tracings improve after two to four months of abstinence from tobacco.

212. The ballistocardiogram would prove useful in the clinical evaluation of bundle branch block from the point of view of the myocardial function; when this function is good the ballistocardiogram is normal. Twenty eight left and eighteen right bundle branch cases are reported.

213. The ballistocardiogram would be important in the diagnosis of myocardial sarcoidosis when there is no heart enlargement and no definite signs of myocardial damage in the electrocardiogram.

214. Coronary and myocardial lesions induced in dogs at different levels and of varying extension always registered an abnormal ballistocardiographic tracing.

THERAPY

215. Intravenous acetylcholine and divalsene used therapeutically in psychic disorders alter the blood pressure figures, the electrocardiogram, and the fundus oculi.

216, 217. Emetine used in therapeutic doses (0.60 to 0.80 Gm. in ten days) is a safe drug. Only 15 per cent of patients showed an inverted T in V_1 and left chest leads and in some cases there was a fall in blood pressure never greater than 15 mm. for the systolic. Experimental work in animals using lethal doses showed an electrocardiographic pattern, with changes in P in repolarization and in intraventricular conduction. Death was caused in 60 per cent of the patients by ventricular fibrillation; autopsy showed degenerative lesions and edema separating the myocardial fibers.

218. The effect of procaine amide in nine individuals with Wolff-Parkinson-White syndrome is discussed. Six of them had some cardiovascular alterations while three were normal. The electrocardiographic picture disappeared in most of them. The only abnormality noticeable was the lengthening of P-R and a slight unusual thickening on the ascending limb of R in the leads which correspond to the left ventricle. This change occurred whether the disease was due to an abnormal pathway from the auricle to the ventricle or to the coupling of the normal sinus rhythm with an abnormal one originating in the upper portion of the septum. This drug would prove useful for differential diagnosis with bundle branch block, coronary thrombosis, or the existence of a dead zone when any of the latter are covered by the Wolff-Parkinson-White electrocardiographic picture.

This syndrome is very often associated with episodes of paroxysmal tachycardia without cardiac structural alteration, although in some instances the

exclusion of such an alteration is very difficult even after vagal stimulation, exercise tests, and the use of several drugs.

219. The value in rheumatic fever of sodium salicylate and ammonium chloride administered rectally over a period of one to twelve days is stressed. This solution can be compared favorably with the oral or intravenous therapy as the effect is immediate and in 65 per cent of the cases the red cell sedimentation rate becomes normal within four weeks. The action is through the hypophyseal-adrenal system with an increase in glucocorticoids secretion and a marked leukopenia which would be more accurate than the salicylate blood level to judge the therapeutic efficacy.

220. Rheumatic carditis is classed as benign, severe, and malignant in accordance with its reaction to therapy. The first responds well to salicylate, 8 to 10 Gm. daily for the first week and in smaller dosages, around 4 Gm. daily, for three months. Cortisone and ACTH shorten the duration. Severe carditis requires 300 to 400 mg. of cortisone the first day and in reducing doses afterwards for one week. ACTH combined with salicylate is given the second week. In malignant carditis cortisone should be given for twelve days in decreasing dosages and ACTH up to 200 ml. for four days thereafter. It is interesting to note that the sedimentation rate may rise during the first two weeks of the steroid therapy.

221, 222. Two other papers deal with the same subject and recommend, for severe cases of rheumatic fever in children with heart enlargement or heart failure, total doses of 2,460 ml. of ACTH or 4,100 ml. of cortisone. Cooperative rheumatic fever studies advise that this treatment should be given in decreasing doses every six hours. In no instance was there retention of sodium or arterial hypertension; eosinophils diminished at first but increased with the progress of the treatment, the signs of heart failure disappeared although rheumatic activity persisted.

223. Para-aminosalicylic acid has been reported as a substitute for salicylate in rheumatic fever because of its antiallergic effect.

224. Experimental work on rats shows that methylthiouracil-induced hypothyroidism stops necrosis caused by femoral artery ligature, increasing tissue resistance to ischemia. Often it is impossible to increase the blood supply in chronic arterial claudication of the limbs. This treatment is based on the decrease of blood supply through antithyroid drugs. Results are not to be expected for several weeks.

225. Human centrifugalization material is used in arteritis obliterans with good result in trophic lesions.

226. Cardiac glycosides decrease the refractory period of the auricle provided the vagal innervation is not altered and a proper anesthetic is used; in denervated heart or in the cardiopulmonary preparation the opposite occurs. The action on the auriculoventricular transmission increases until a complete block sets in. The refractory period of the ventricle is also decreased until toxic concentrations are approached, and ventricular fibrillation may be induced.

227. The death in intoxication by cardiac glycosides is due to ventricular fibrillation caused possibly by a decrease of the intraventricular conduction and an increase of the automatism of the ventricle. On the other hand the death caused by cardiac genins is generally due to diastolic ventricular arrest, without fibrillation possibly because the genins decrease the ventricular automatism in opposition to the glycosides. Experimental work on isolated frog hearts and on cardiopulmonary preparation is described.

228. The action of ouabain, Digitoxin, Digilanid and Cedilanid on the cardiopulmonary preparation with ventricular overload is explored. The usual therapeutic dosages did not alter the output; at times toxic doses of ouabain induced a fall in the heart rate and heart block with probably secondary small deviations (either positive or negative) of the output. Cardiac depression by anesthetics impairs the detection of a superimposed digitalis action.

229. Digitalis would have a similar action on the ordinary skeletal muscle with insufficient blood flow as on the insufficient myocardium. The use of oxygen and of other elements essential for muscular exertion is improved.

230. In 100 patients submitted to intensive digitalization for heart failure, the pulse rate and circulation time were reduced simultaneously or successively, although in a large percentage (49 per cent) the chronotropic and inotropic action were dissociated. In 19 per cent there was no change in either heart rate or circulation time. The usefulness of circulation time to evaluate the action of the drug is emphasized.

231. Acidophil cells in peripheral blood are determined before and after digitalization, before and after the intravenous injection of 1 mg. of Atropine in normal individuals and in patients with congestive heart failure. The possible causes of increase or decrease are discussed.

232. Oleandrin is a glycoside of strophanthin and probably composed of gitoxigenin and digitalose, thus differing from Digitalinum verum by the loss of a glucose molecule. Its cardiotonic and diuretic action by mouth is similar to that of digitalis and strophanthin but more efficacious and faster in acute cardiac emergencies in daily doses of 0.4 to 1.2 mg.

233. The use by slow intravenous injection of a combination of 0.5 mg. of ouabain, 0.08 of theophylline or 0.24 of aminophylline and 0.10 of procaine or novocaine in 20 c.c. of 50 per cent glucose is advocated in acute pulmonary edema when the usual treatments have failed. Procaine is a sympathicolytic and somatolytic agent that diminishes pain, reduces myocardial irritability, and is secreted by the kidneys within 20 minutes and destroyed quickly by the liver. It is also antiallergic and free from side effects.

234. In congestive failure, refractory to intensive treatment with precipitating and aggravating factors such as anemia, thyrotoxicosis, myxedema, beriberi, hepatic cirrhosis, pulmonary disease, pericardial constriction, and arteriovenous fistulas should be ruled out. Antidiuretic drugs such as sedatives should be controlled. Occasionally hypochloremic alkalosis, hyponatremic acidosis, or hypertonic dehydration are found. Dietary restriction such as the 200 mg. low sodium diet results in inadequate intake of proteins and vitamins.

The restriction of the sodium intake and the use of mercurial diuretics may produce excessive loss of sodium and chlorides. Hypotonic dehydration and excessive water ingestion during sharp protein intake restrictions are rare and of questionable significance. Mercurial tubular poisoning preventing the conservation of bases occasionally occurs. Nephrotic edema or glomerulitis shows diminishing response to mercurials; hypoproteinemia and anuria may result. Electrolytic disbalance should be corrected before it becomes irreversible.

235. Lanatoside C, (1.8 mg. intravenously) in patients with congestive failure caused a slight rise of glomerular filtration and ERPF rate. Perhaps because the effect of intravencus saline is exaggerated in those who are already overloaded with sodium, there was a conspicuous fall in the reabsorption factor for sodium after about 30 minutes, indicating a decrease in the tubular reabsorption while the rate of reabsorption per cubic centimeter of effective renal plasma flow rose slightly, probably as a result of the decreased stasis in the peritubular capillar plexus.

Mercaptomerin in 2 c.c. (80 mg. of Mercury) intravenous doses in the same patients caused a decrease in glomerular filtration while the effective renal plasma flow was usually somewhat decreased and the reabsorption factor for sodium was conspicuously decreased and the rate of reabsorption per cubic centimeter of effective renal plasma flow was slightly decreased.

Aminophylline (250 mg.) given intravenously in similar patients increased mildly the glomerular filtration rate and the reabsorption factor for sodium, indicating that it works through an improvement of circulation without direct effect on the tubules and with only slight and transient action on the glomerulus.

236. Three individuals with heart disease were prescribed mercurial diuretics and an acute urinary retention followed. The pathogenesis and relationship to the drug and possible prevention are discussed.

237, 238, 239. Three papers deal with the cationic exchange resins used exclusively or accompanied with mercurial diuretics and digitalis in congestive heart failure with edema, cirrhosis with ascites and edema, nephrotic syndrome, and essential hypertension. The results were better when a low-sodium diet of 700 to 800 mg. was associated. Edema and weight were greatly reduced and the diuresis increased, occasionally the mercurial diuretics were potentiated. A nephrotic syndrome showed a tendency to acidosis and hypoptassemia which disappeared with the omission of the drug.

240, 241. Experiments on dogs, rabbits, and turtles lead one to believe that procaine amide (Pronestyl) is a colinergic drug useful in experimental arrhythmias except ventricular fibrillation. The drug was more efficient clinically in ventricular arrhythmias and auricular arrhythmias recently acquired. It usually fails in long standing fibrillation and flutter. Its indications and mechanism of action are discussed.

242. Quinidine blood levels were established experimentally in dogs and in human beings. Whether given in a single or separate doses the curves were

similar to those of salicylate therapy. The administration at 12-hour intervals would give a uniform plasma concentration level. Fifty per cent of auricular fibrillation cases were restored to normal rhythm.

243. Another paper gives a 60 per cent conversion figure following Katz and Levine's scheme. Some were long standing fibrillations with enlargement of the heart and congestive failure; others had complete or incomplete bundle branch block. The most common electrocardiographic changes induced by quinidine were a decrease of ventricular rate, an increase of auriculoventricular or intraventricular conduction, auriculoventricular block and changes in the ST-T segments. Out of seventy patients three died, one from cinchonism and two from emboli.

244. Experimental work on rats with hypothyroidism induced by methylthiouracil proved they were resistant to the inducement of ventricular tachycardia by intravenous calcium chloride. This led to the use of antithyroid drugs in paroxysmal tachycardia cases in which hyperthyroidism had been discarded. Auricular fibrillations and supraventricular tachycardia were treated with excellent results whether they were of hypertensive, coronary or rheumatic etiology or without demonstrable cardiovascular lesion. Results should not be expected for some time and high dosages up to 1 grain of methylthiouracil daily should be used over a long period. No serious mishaps occurred.

245. Anticoagulants were widely discussed. On 300 individuals in Mexico with myocardial infarcts treated without anticoagulants there was a 10 per cent mortality within the year. This has been lowered to 6 per cent since uncomplicated cases are got up 24 hours after the onset of the disease. These statistics would be more favorable than those for patients treated with anticoagulants. On the other hand, this author believes it is antiphysiologic to use these drugs because they disturb the healing of the ischemic necrobiosis and may favor the disintegration of the intraventricular thrombus when it exists, produce emboli, and delay the final state of sclerosis which is reached through coagulation of the blood infiltrated between the muscular bands.

246. A paper on the relation of the incidence of thromboembolic phenomena to treatment in acute coronary occlusion was based on a series of 983 cases with a mortality of 45 per cent. The lowest mortality (26 per cent) was in a group treated with erythrityl tetranitrate alone or combined with other drugs, and the highest (72 per cent) in groups which had received no treatment. Seven per cent showed clinical evidence of emboli and in 133 autopsies emboli were found in 30 per cent. The lowest percentage was in the groups treated with papaverine, anticoagulants, and erythrityl.

247, 248. Experience in New York with the new anticoagulants Tromexan, Phenilindanedione, Compound 63, and Paritol was reported. Two hundred and sixty-six patients were maintained on Dicumarol or Tromexan for periods from one month to six years with careful control of prothrombin time. The diagnoses were as follows: Rheumatic heart disease with emboli, 11 per cent; recurrent local or migratory phlebitis, 54 per cent; recurrent coronary thrombosis, 28 per cent; occlusive arterial disease and miscellaneous thrombotic states, 7 per cent.

249. Another paper with follow-up over four years in Brazil deals with the same subject. It stresses that the bleeding complications (epistaxis, blood in urine and stools) stop early with the discontinuance of the drug and allergic reactions to heparin disappear spontaneously with repeated injections combined with antihistamines. There was no bleeding in many cases with prothrombin time above 90 seconds and up to 150 seconds. The treatment works not only because of the anticoagulant action but also due to a vasodilator and antiallergic effect. In severe cases of congestive heart failure Dicumarol prevented thrombo-embolic accidents.

250. Six years of experience at the National Institute of Cardiology of Mexico are given: fatal hemorrhages occurred in three cases of bacterial endocarditis: Two treated with heparin and one with Dicumarol. Liver function was normal after six months of treatment and major surgery was performed while prothrombin time was prolonged.

251. The value of Tromexan, at lower dosages than those generally advocated, as a drug of very quick action with a rapid return of prothrombin time to normal after its omission is enhanced.

252. A comparative study of Tromexan and Dicumarol in thrombo-embolic diseases was performed controlling the treatment with prothrombin time, microscopic hematuria, and resistance to heparin in vitro.

253. A series of one hundred cardiovascular syphilitic patients has been followed over five years in Peru and treated with penicillin. Although five died; four of heart failure and one of a ruptured aneurysm, in general results were excellent, and one patient with coronary disease in which arsenic, bismuth and mercury produced a severe Herxheimer reaction had a perfect tolerance. The treatment, if needed, may be given conjointly with the usual one for heart failure.

254. Another paper advocates alternate treatment with penicillin and bismuth in twenty cases of syphilitic aortitis with or without aortic insufficiency. Penicillin (7,500,000 U.) and twenty injections of Lyposoluble, with bismuth twice a year for two years were recommended. Improvement was remarkable.

SURGERY

255, 256, 257. Surgical treatment of *mitral stenosis* increases the size of the mitral orifice to 1½ or 2 cm. within fifteen days. There is also a fall in the pulmonary pressure and in the right ventricular diastolic pressure although the vascular pulmonary resistance is not changed.

258. A series of thirteen cases treated with surgery from 1950 to 1952 is reported. There were three deaths; one from auricular tearing and two from brain embolism. The longest survival to date is 22 months. Dyspnea on effort disappeared completely in two cases of rheumatic cor pulmonale.

259. Surgical treatment should be recommended in patients between 20 and 45 years without rheumatic activity or associated significant valvular lesions or when there is venous pulmonary congestion. Auricular fibrillation or cardiac enlargement are not counter-indications but right ventricular failure is a definite one as in these cases heart failure recurs and the risk is too great for a temporary

improvement. Usually after surgery there is a decrease in the size of the heart, especially of the left auricles the right-axis deviation diminishes and there is an increase in the vital capacity and the circulation time. There is also a fall in the pressure in the right ventricle and the pulmonary artery but smaller than one would expect in view of the clinical improvement. The heart murmurs at first disappear for several weeks and then reappear. They are mid-diastolic and a thrill appears, notwithstanding the clinical improvement. There are cases reported which develop mitral insufficiency after the operation but improve clinically.

260, 261, 262, 263. *Constrictive Pericarditis.* Thirty patients have been observed over a period of 11 years, of which eighteen have been treated surgically. Criteria for selection of cases and the importance of preoperative streptomycin are emphasized. Hemodynamic studies can certify the diagnosis in doubtful cases and help to localize the zone where the constriction is more marked. Catheterization has also proved the relative importance of interference with diastolic filling of the ventricles as opposed to obstruction of cardiac filling at the level of the venae cava and the atria and the importance of constriction at the left heart chambers indicated by the elevated pulmonary artery and pulmonary capillary pressures. These pressures return toward normal after surgery. There is also a decrease in right auricular pressure and an increase in cardiac output. Postoperatively the acute failure due to absorption of retained fluids must be kept under control and the kidneys and liver carefully watched.

264. Twenty patients with arteriosclerotic aneurysm of the abdominal aorta confirmed by aortography came to surgery. Thirteen patients died. Wiring was used in nine cases, partial ligation with rubber band and Cellophane in four, vein graft in five, and spleno-iliac by-pass in one. Pathological examinations demonstrated the deficient vascular supply to the wall of the aorta and the necrotic character of the aneurysmal lining. Therefore in the future replacement of the diseased wall of the aneurysm by viable vascular structure is suggested.

265. The following conclusions are based on the experience with 190 cases of congenital heart disease:

A. *Acyanotic group*: (1) Persistence of the arteriovenous ductus. Surgery advised when there is no electric deviation of the axis to the right, preferably after the age of two and at any age if there is subacute bacterial endocarditis or heart failure. Double ligation is the choice. (2) Coarctation of the aorta following the Crafoord-Gross technique and only when angiography shows it to be extreme or total and not extensive.

B. *Cyanotic group*: (1) Fallot and Corvisart use surgery after three and before this age if there are frequent episodes of dyspnea and cyanosis or if the red cell count is above 8 million, (Taussig-Blalock's operation). (2) Pulmonary stenosis with closed ventricular septum (Brock's operation performed without success whatever the age.) (3) Tricuspid atresia recognized by left-axis deviation. Taussig's operation was recommended, also in dextrocardia and levocardia with decreased pulmonary circulation. (4) Total transposition of the large vessels and pseudo-truncusarteriosus, when surgery has failed.

266. Two operations performed by the Crafoord technique in coarctation of the aorta are reported, one on a patient aged 17 who died shortly after, while the other, aged 8, recovered.

267. Other surgical statistics in Buenos Aires are as follows: (1) Eighty-five with persistent ductus arteriosus, five died. (2) One hundred-five with tetralogy of Fallot, twenty died. The ideal age for surgery would be around six. (3) Five with pulmonary stenosis of whom two survived with great increase in functional capacity. (4) Transposition of the large vessels, six unsuccessful cases. (5) Fifteen with thoracic aortic coarctation; three dead and twelve alive with reappearance of the femoral and pedal pulse and normal blood pressure. (6) One of abdominal coarctation in which a graft of preserved artery was inserted. He died because of an associated hypoplasia of the renal arteries.

268. In Fallot's tetralogy the symptoms are caused mainly by the pulmonary stenosis and the dextroposition of the aorta; the former causes the veno-arterial shunt and therefore all the symptoms of the malformation. The organism adapts anatomically through the patent ductus arteriosus and the bronchial collateral circulation. The Blalock-Taussig operation reproduces this adaptation and should be, therefore, the operation of choice. Brock's operation on the other hand does not attempt to alter the dextroposition of the aorta and may change the Fallot to an Eisenmenger complex which cannot be corrected.

269. Experience with 44 patients treated with surgery for acquired cardiopathies is reported. In constrictive pericarditis there were good results using bilateral transverse incision and a one-stage operation. Resection without drainage was performed in recurrent exudative pericarditis. Resection of the thoracocervical sympathetic nerves and of the cardiac plexus in angina pectoris was a failure and suggests the advisability of repeated blockages. Ligature of the lower vena cava, total thyroidectomy, or cholecystostomy in persistent heart failure proved satisfactory. In mitral stenosis results are encouraging.

270. Another paper deals with the results of the ligature of the lower vena cava or minor veins in the treatment of congestive failure, unresponsive to medical treatment.

271, 272. Experimental work on interruption of circulation, its maintenance by artificial media, and its repercussion on the heart and the brain are reported. The circulation is interrupted by occlusion of (1) both venae cava, (2) aorta, (3) pulmonary artery or overloading the heart through stenosis of the pulmonary artery. The perfusion of the coronary arteries prevents death of the heart in dogs and allows the heart to deal better with unfavorable hemodynamic situations. The perfusion of the coronary arteries was used in men; the technique and results are detailed.

273. Experimental work was performed in dogs by placing a permanently based pedicle skin flap on the myocardium and a rich macroscopical anastomic circulation can be demonstrated between the arteries of the pedicle flap and the coronaries. One month later these animals have survived ligation of the anterior desending branch of the left coronary artery.

PAPERS SUMMARIZED

185. Espino Vela, J., and Sodi-Pallares, D.: Electrocardiographic Diagnosis of Valvulopathies, Mexico, D. F.
186. Posteli, T., Garbini, G. C., and Todesco, M.: Electrocardiographic and Photoplethysmographic Effects of Some Substances With a Trophoenzymatic Action, Bologna, Italy.
187. Herve, L., Sotomayor, A., and Moraga, H.: Results of Arterial Pressure Variations and Heart Rhythm Frequency on the ECG After Effort, Santiago, Chile.
188. Durrer, D.: The Spread of the Electrical Impulse Through the Myocardium, Amsterdam, Holland.
189. Sodi-Pallares, D., and Rodriguez, M. I.: Method for Studying the Sequence and Speed of the Process of Activation on Dog Ventricles. Evaluation of the Method, Mexico, D. F.
190. Rodriguez, M. I., Sodi-Pallares D., and Anselmo Ch., A.: Activation of Free Ventricular Walls on Dog's Heart, Mexico, D. F.
191. Barbato, E., Décourt, L. V., and Pileggi, F.: A Study on the Ventricular Excitation of the Human Heart. I. The Spread of the Stimulus in the Normal Heart, São Paulo, Brazil.
192. Barbato, E., Décourt, L. V., and Pileggi, F.: A Study on the Ventricular Excitation of the Human Heart. II. The Spread of Stimulus in the Pathologic Heart São Paulo, Brazil.
193. Zapata, J., and Diaz de León, L.: ECG Modifications in Experimental and Clinical Acute Pulmonary Edema (APE), Mexico, D. F.
194. Villareal, H., Tranchesi, J., Maldonado, G., and Benavides, P.: ECG in Electrolytic Alterations and Acid-base Balance of the Blood, Mexico, D. F.
195. Gomez Hernandez, A., Calvino, J. M., Larreondo, F., Rosales, V., Inigo, J. R., and Ledon, F.: ECG Alterations of the Cardiac Tamponage Produced by Pericardiac Overflow (Hydro- and Hemo-pericardium). Experimental Study, Havana, Cuba.
196. Chait, L. O., Campos, F. C. M., and Tranchesi, J.: Electrocardiographic Study of Ventricular Hypertrophies Consecutive to Stenosis Experimentally Provoked in the Descending Aorta, Mexico, D. F.
197. Rodriguez, M. I., and Sodi-Pallares, D.: Mechanism of Bundle Branch Block, Mexico, D. F.
198. Zuckermann, R., Cisneros, F., and Medrano, G. A.: Conduction Disorders in the Chicken Heart, Mexico, D. F.
199. Velasco Lombardini, R., Rivero, C. H., and Balestrino, R.: The Sino-auricular-ventricular Connection, Montevideo, Uruguay.
200. Gonzalez Sabathié, L., Robiolo, O. A., and Leone, L. E.: A New Model of Ballistocardiograph and Its Advantages in Clinical Use, Rosario, Argentina.
201. Frankel, Alan L.: The Clinical Value of Ballistocardiography, Cleveland, Ohio, U. S. A.
202. Gonzalez Sabathié, L., Robiolo, O. A., and Leone, L. E.: Ballistocardiography in the Normal Child, Rosario, Argentina.
203. Gonzalez Sabathié, L., Robiolo, O. A., and Leone, L. E.: The Normal and Pathological Ballistocardiogram in the Adult, Rosario, Argentina.
204. Gonzalez Sabathié, L., Robiolo, O. A., and Leone, L. E.: Ballistocardiography in Pregnancy, Rosario, Argentina.
205. Rojas Villegas, F., del Campo, E., Falgarete, P., Brailovsky, D., and Manubens, S.: The Normal Ballistocardiogram, Santiago, Chile.
206. Rojas Villegas, F., del Campo, E., Falgarete, P., and Brailovsky, D.: The Pathological Ballistocardiogram, Santiago, Chile.
207. deSoldati, L., Mejia, R. H., and Avellaneda, M.: Early Diagnosis of Coronary insufficiency Through the Use of the Ballistocardiogram and of Discriminative Precordial Leads of the Electrocardiogram, Buenos Aires, Argentina.
208. deSoldati, L.: The Ballistocardiogram in the Diagnosis, Evolution and Prognosis of Certain Cardiopathies, Buenos Aires, Argentina.
209. Navarro Viola, R.: Action of Certain Drugs on the Ballistocardiogram of Normal Subjects and on Various Pathological Conditions, Buenos Aires, Argentina.
210. Barrera, F., Ruiz Leiro, A., Bustamente, R., and Kaufman, J.: Comparative Study of Electrocardiograms and Ballistocardiograms Taken Directly From the Body in Coronary Artery Disturbances, Havana, Cuba.
211. Mandelbaum, H., and Mandelbaum, R. A.: The Ballistocardiograph as a Means of Detecting Nicotine Sensitivity, Brooklyn, N. Y., U. S. A.
212. Mandelbaum, H., and Mandelbaum, R. A.: Ballistocardiographic Studies in Bundle Branch Block, Brooklyn, N. Y., U. S. A.
213. deSoldati, L., Doyle, J., and Navarro Viola, R.: The Ballistocardiograph in the Detection of Heart Disturbances of Carcoidosis, Buenos Aires, Argentina.
214. Cossio, P., Berreta, J. A., Mosso, H. E., and Perianes, I.: The Ballistocardiograph in Experimental Myocardiac Aggression, Buenos Aires, Argentina.

215. Fernandez, J. B.: Heart Alterations Provoked by Strong Doses of Acetylcholine and Divalsene, Porto Alegre, Brazil.
216. Taboada Millás, C. A., Jay, L. F., and Edelstein, J.: Cardiovascular Action of Emetine, Havana, Cuba.
217. Taboada Millás, C., Perez Mesa, C., Arias Leon, L., Jay, L. F., and Edelstein, J.: ECG Alterations Determined by Emetine, Havana, Cuba.
218. Villamil, A., Franco, R. J., and Sarruff, M.: Clinical and Electrocardiographic Study on 11 Cases of Wolff-Parkinson-White Syndrome, Buenos Aires, Argentina.
219. Pasqualini, R. Q., and Spirito, E.: The Election and Control of the Treatment of Rheumatic Fever, Buenos Aires, Argentina.
220. Herrera Ramos, F.: The Treatment of Rheumatic Carditis. Handling and Scope of New Therapies, Montevideo, Uruguay.
221. Kreutzer, R., Caprile, J. A., Wessels, F., Berri, G. G., and Gonzalez P., A. D.: ACTH and Cortisone in Rheumatic Carditis of Children, Buenos Aires, Argentina.
222. Bolívar Delgado Correa: Treatment of Rheumatic Carditis in Children With Cortisone and ACTH, Montevideo, Uruguay.
223. Kirschbaum, M.: Treatment of Rheumatic Fever with PAS (para-amino-salicylic acid), Tucuman, Argentina.
224. Malamud, B., Battle, F., and Malinow, M. R.: Treatment of Chronic Obliterating Arteriopathies of the Extremities With Antithyroid Drugs, Buenos Aires, Argentina.
225. Velasco Lombardini, R., Isasi, E. J., and Enaya, E. D.: The Treatment of Arteritis Obliterans by Human Centrifugalization, Montevideo, Uruguay.
226. Méndez, R., and Méndez, C.: Action of Cardiac Glycosides on the Refractory Period of the Heart Tissues, Mexico, D. F.
227. Méndez, R., Nava, A., and Méndez, C.: A Comparative Study of Certain Cardiac Glycosides and Their Genins, Mexico, D. F.
228. Duomarco, J. L., Giambruno, C. E., and Stable, J. E.: Action of the Digitalic Bodies on the Heart-lung Preparation With Ventricular Overload (Second Communication), Montevideo, Uruguay.
229. Méndez, L., and Macossay, C.: Digitalization of the Ischemic Skeletal Muscle, Mexico, D. F.
230. Arrighi, F. P., Piaggio, A. A., Sonnemberg, M., Restano, F. S., Gonella, C. G., Calniquer, M., and Mora, J. E.: Digitalic Tonification and Bradycardization, Buenos Aires, Argentina.
231. Delle Vedova, A.: Eosinophilia in Digitalized Heart Patients, Rosario, Argentina.
232. Kandalla, F. A.: Oleandrin in Acute Cardiac Emergencies, Baghdad, Iraq.
233. Kandalla, F. A.: Ouabain, Theophyllin, Procaine and Glucose in Acute Pulmonary Edema, Baghdad, Iraq.
234. Herrmann, G. R., and Herrmann, H. C., (with chemical analytical assistance of Russell, A. Y.): A Study of Heart Failure Refractory to Treatment, Galveston, Texas, U. S. A.
235. Herrmann, H. C., Herrmann, G. R., and Russell, A. Y.: Renal Function Studies After Intravenous Administration of Digitalis Mercaptomerin and Theophyllin, Galveston, Texas, U. S. A.
236. Gutiérrez Márquez, R.: Acute Urine Retention During Therapy With Mercurial Drugs, Rosario, Argentina.
237. deSoldati, L., and Montoreano, F.: Action of Cationic Exchange Resins in Arterial Hypertension, Congestive Cardiac Insufficiency and Edemas of Other Etiologies, Buenos Aires, Argentina.
238. Markman, A., Schwartz, A., and Barbosa Correa, C.: Cation Exchange Resins and Their Use in the Control of Edema, São Paulo, Brazil.
239. Gonzalez, J. M., Gonzalez Garcia, J., Sozzi, C., and Gallo, J. F. N.: Ion Exchange Resins in the Therapy of Edemas, Rosario, Argentina.
240. deSoldati, L., and Rabenko, J.: Results Obtained Through the Use of Pronestyl in the Treatment of Supraventricular and Ventricular Arrhythmia, Buenos Aires, Argentina.
241. Taboada Millás, C., Rodriguez Iñigo, J., Fernández Ledón, R., Ugarriza, L., Jay, L. F., and López, A.: Clinical and Experimental Evaluation of Procanimide, Havana, Cuba.
242. Cesarman V., T., and Tremar, C.: Contribution to the Study of Quinidine Therapy, Mexico, D. F.
243. Lamas, D., Florenzano, R., and Chamorro, G.: Treatment of Chronic Auricular Fibrillation With Quinidine, Santiago, Chile.
244. Battle, F. F., Malamud, B., and Malinow, M. R.: Treatment of Paroxysmal Tachycardias With Antithyroid Drugs, Buenos Aires, Argentina.
245. Govea, J.: Antiphysiological Action of Anticoagulants in Myocardial Infarction, Havana, Cuba.
246. Kissane, R. W., Fidler, R. S., and Conn, J. J.: The Relation of the Incidence of Thromboembolic Phenomena to Treatment in Acute Coronary Artery Occlusion, Columbus, Ohio, U. S. A.

247. Wright, I. S.: An Evaluation of the Newer Anticoagulants, New York, U. S. A.
248. Foley, W. T., and Wright, I. S.: Long-term Anticoagulant Therapy, New York, U. S. A.
249. Mayall, R. C.: Use of Anticoagulants in Cardiovascular Diseases, Rio de Janeiro, Brazil.
250. Méndez, L., Zajarías, S., and Maldonado, G.: Handling of Anticoagulants: Six Years' Experience at the National Institute of Cardiology of Mexico, Mexico, D. F.
251. Avallaneda, M., Castro, C. M., and Stritzler, G.: Regarding the Action of Tromexan on Normal Subjects and Various Pathological Conditions, Buenos Aires, Argentina.
252. Garcia Turiella, R., Gaspary, F. V., Tuero, P. R., and Ferrer, J.: Our Experience With Tromexan, Rosario, Argentina.
253. Peralta V., A., Castañeda P., L., Galdós H., R., Bocanegra A., J., Bendezú P., J., and Cheesman J., R.: Penicillin Therapy in Cardiovascular Syphilis. Results of Six Years of Observation, Lima, Peru.
254. Etcheves, J. C., Becker, L., and Gragnolino, J.: Treatment of Syphilitic Aortitis With Penicillin and Bismuth, Buenos Aires, Argentina.
255. Dexter, L., Lewis, B. M., Gorlin, R., Houssay, H. E. J., and Haynes, F. W.: Physiologic Evaluation of Patients With Mitral Stenosis Before and After Mitral Valvuloplasty, Boston, Mass., U. S. A.
256. Ferreyra Santos, R.: Observations on Surgical Treatment of Mitral Stenosis, São Paulo, Brazil.
257. Zerbini, E. J., Borges, S., Ratto, O., Ramos, O., Losso, L., Yunes, A., Nicolai, A., Portugal, O., and San Juan, E.: Indication and Follow-up of Mitral Commissurotomy, São Paulo, Brazil.
258. Taquini, A. C., Tricceri, F., Lozada, B. B., Donaldson, R. J., and d'Aiutolo, R. E.: Immediate and Remote Results of Valvuloclasia of the Mitral Valve, Buenos Aires, Argentina.
259. Bustamante, R. A., Barrera, F., Macías Castro, I., Casas Rodriguez, R., and Perez Stable, A.: Results of Surgical Treatment of Mitral Stenosis, Havana, Cuba.
260. Alessandri R., H., de Amesti, F., and Florenzano G., R.: Chronic Constrictive Pericarditis, Santiago, Chile.
261. Limón Lasón, R., Rubio Alvarez, V., and Bouchard, F.: Constrictive Pericarditis: A Study Carried Out by Means of Intracardiac Catheterization, Mexico, D. F.
262. Friedlich, A. L., Scannell, J. G., Myers, G. S., and White, P. D.: The Significance of Pulmonary Hypertension in Constrictive Pericarditis, Boston, Mass., U. S. A.
263. Gibert-Queralto, J., Paravisini-Parra, J., Torner-Soler, M., Morato-Portell, M., and Gregorich-Servat, A.: Functional Exploration as an Orientation for the Treatment of Constrictive Pericarditis, Barcelona, Spain.
264. Freeman, N. E., Carr, J. L., Fullenlove, T. M., Leeds, F. H., and Crellin, H.: Pathological Characteristics and Surgical Treatment of Arteriosclerotic Aneurysms of the Abdominal Aorta, San Francisco, Calif., U. S. A.
265. Kreutzer, R., Caprile, J. A., Wessels, F., and Berri, G. G.: Congenital Heart Diseases Susceptible to Surgical Treatment, Buenos Aires, Argentina.
266. Taiana, J. A., Schieppati, E., and Leva, A.: Cardiovascular Surgery, Buenos Aires, Argentina.
267. Albanese, R. A.: Surgery in Congenital Heart Diseases, Buenos Aires, Argentina.
268. deCarvalho Azevedo, A., and Hilario, J.: Physiological Basis of the Surgical Treatment of Fallot's Tetralogy, Rio de Janeiro, Brazil.
269. Albanese, A. R.: Surgery of Acquired Cardiopathies. Forty-four Operations, Buenos Aires, Argentina.
270. Berreta, J. A., and Perianes, I.: Ligation of the Inferior Vena Cava and Venous Ligations in the Treatment of Cardiac Failure, Buenos Aires, Argentina.
271. Perianes, I., Berreta, J. A., and Calvo, R.: Attempts on the Maintenance of Artificial Circulation, Buenos Aires, Argentina.
272. Perianes, I., Berreta, J. A., and Calvo, R.: Attempts on the Maintenance of Artificial Circulation, Buenos Aires, Argentina.
273. Lord, J. W., Jr., vonWedel, J., Stone, P. W., Neumann, Ch. G., Hinton, J. W., and Moran, R. E.: Revascularization of the Heart by a Pedicle Skin Flap. An Experimental Study, New York, U. S. A.

INDEX TO VOLUME 46

AUTHORS INDEX

D

E

F

G

H

SUBJECT INDEX

A

B

upy.

kies,
s are
dian-
e for

tored
table